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The American Journal of Medicine

VOL. IX JULY, 1950 No. 1

Editorial

Clinical Studies

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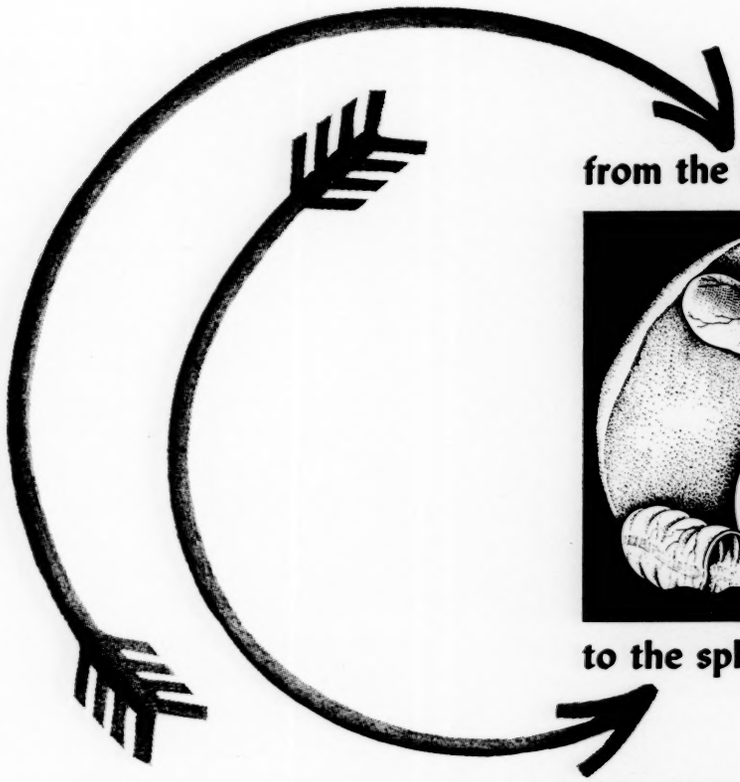
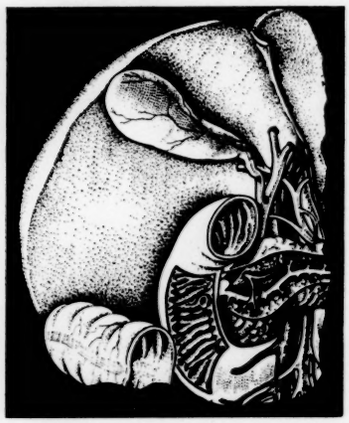


from the liver parenchyma



to the sphincter of Oddi

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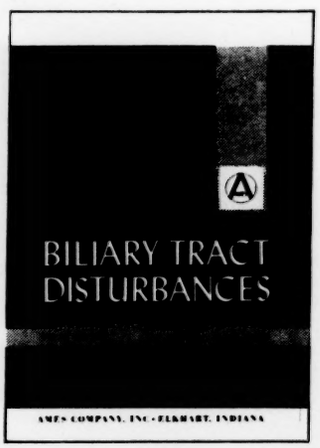

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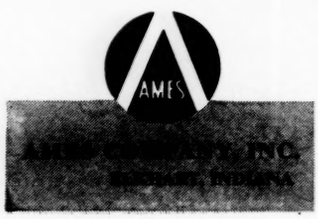

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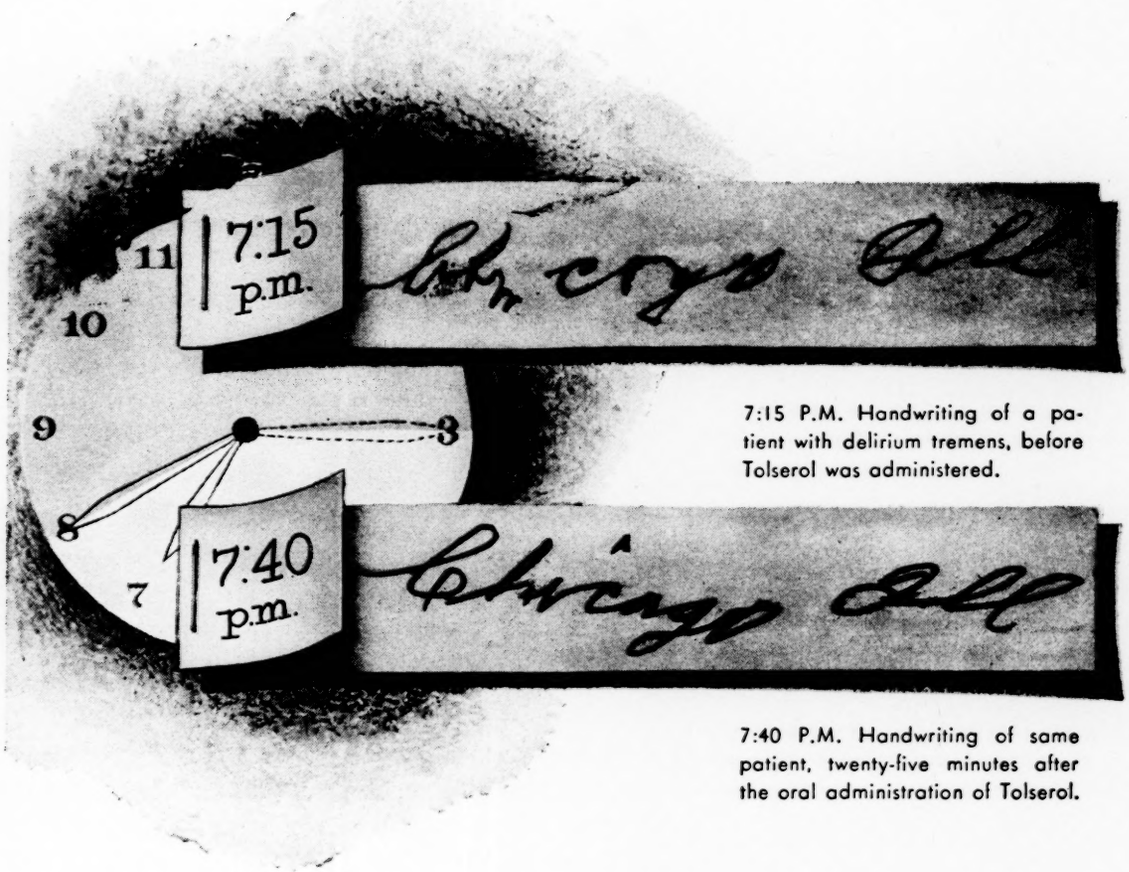

7:15 P.M. Handwriting of a patient with delirium tremens, before Tolserol was administered.

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rational therapy

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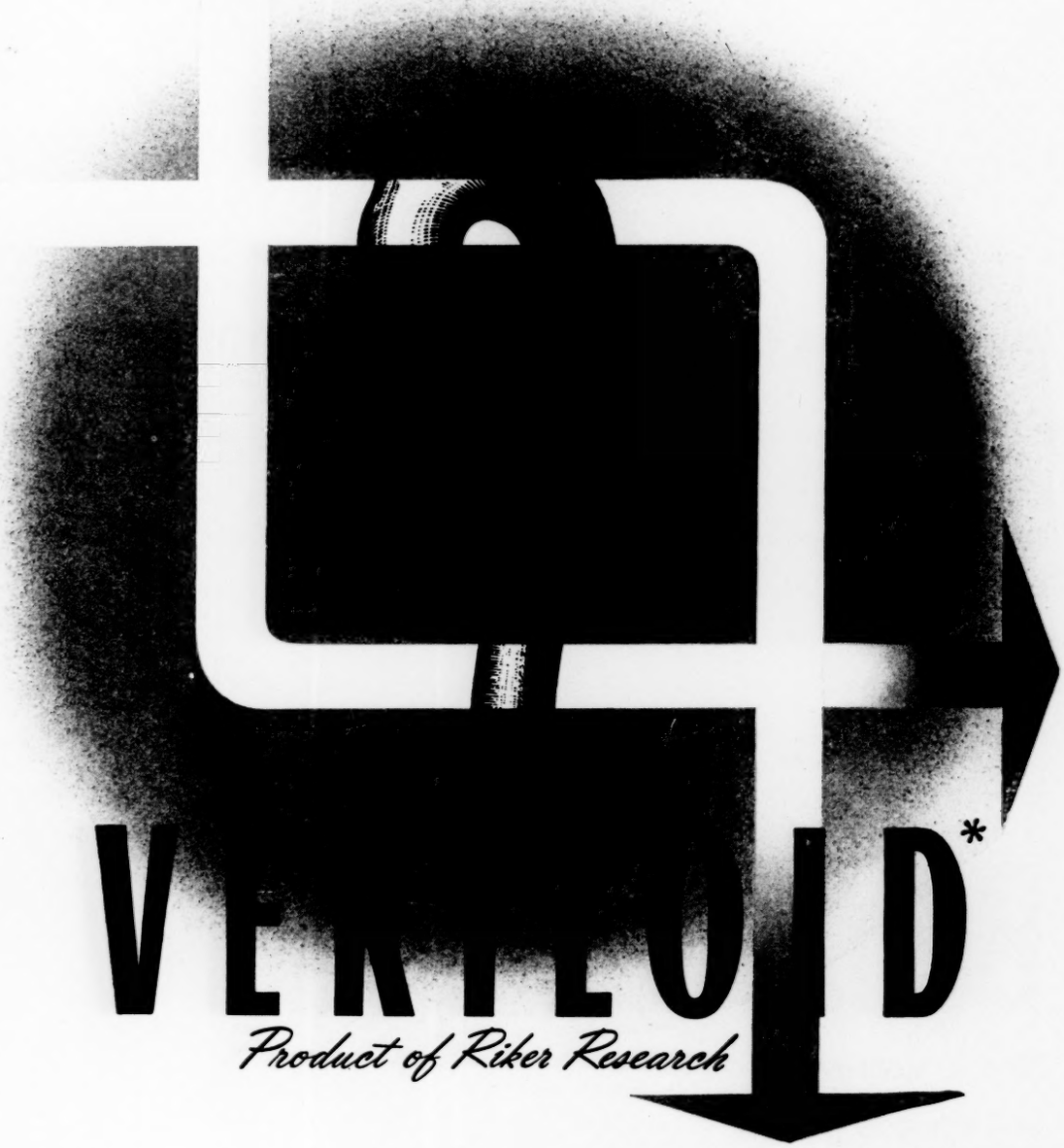

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Wilkins, R. W.; Stanton, J. R., and Freis, E. D.: Essential Hypertension, Therapeutic Trial of Veriloid, a New Extract of Veratrum Viride, Proc. Soc. Exper. Biol. & Med. 72:302 (Nov.) 1949.

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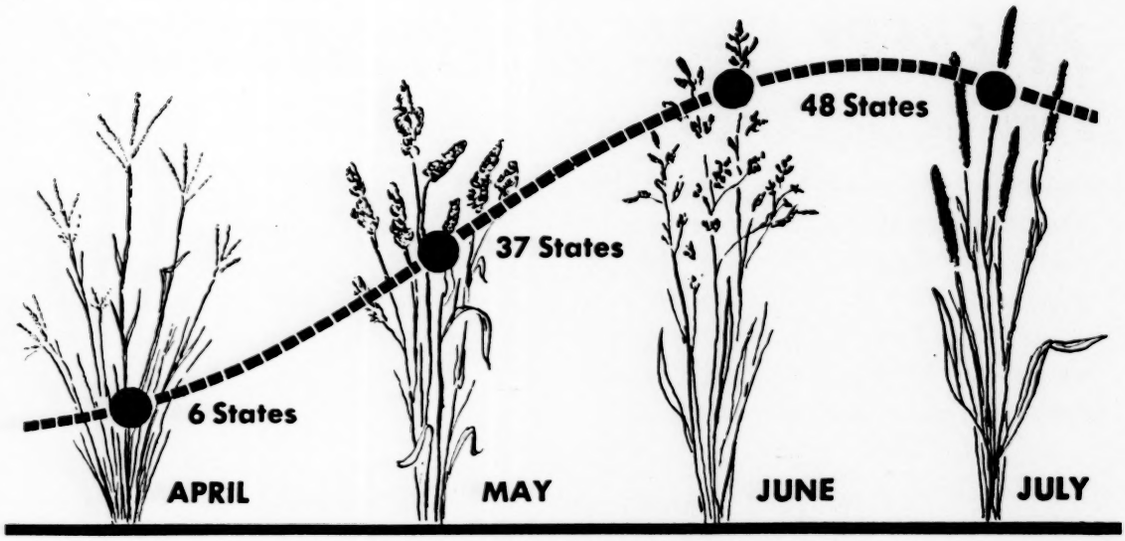

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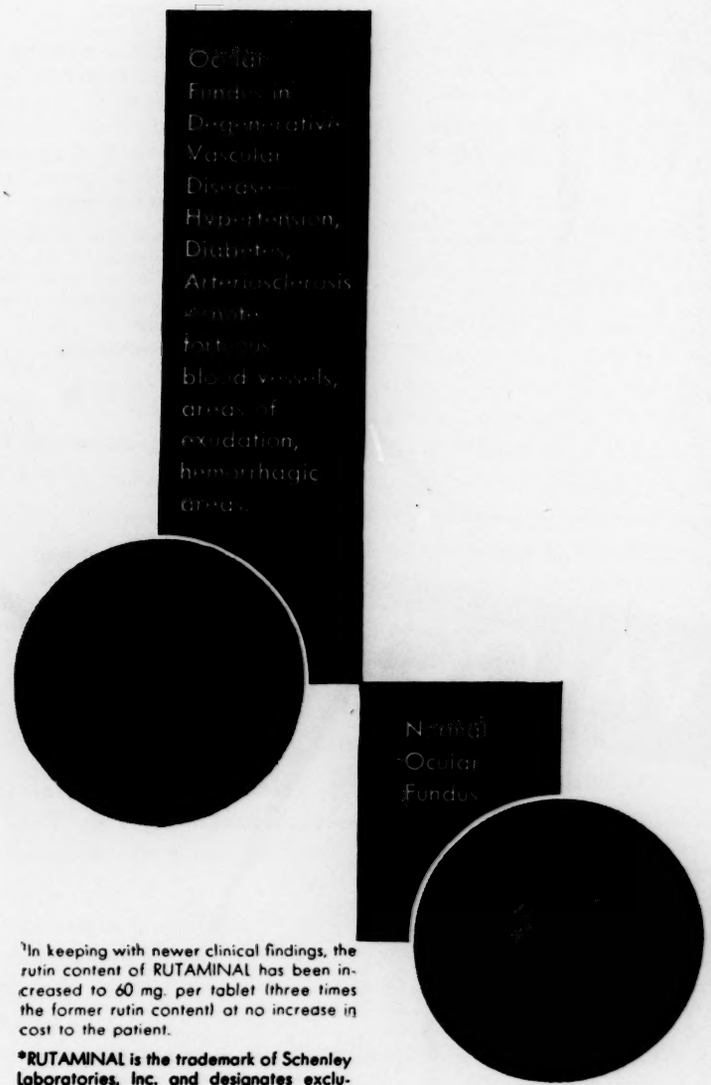

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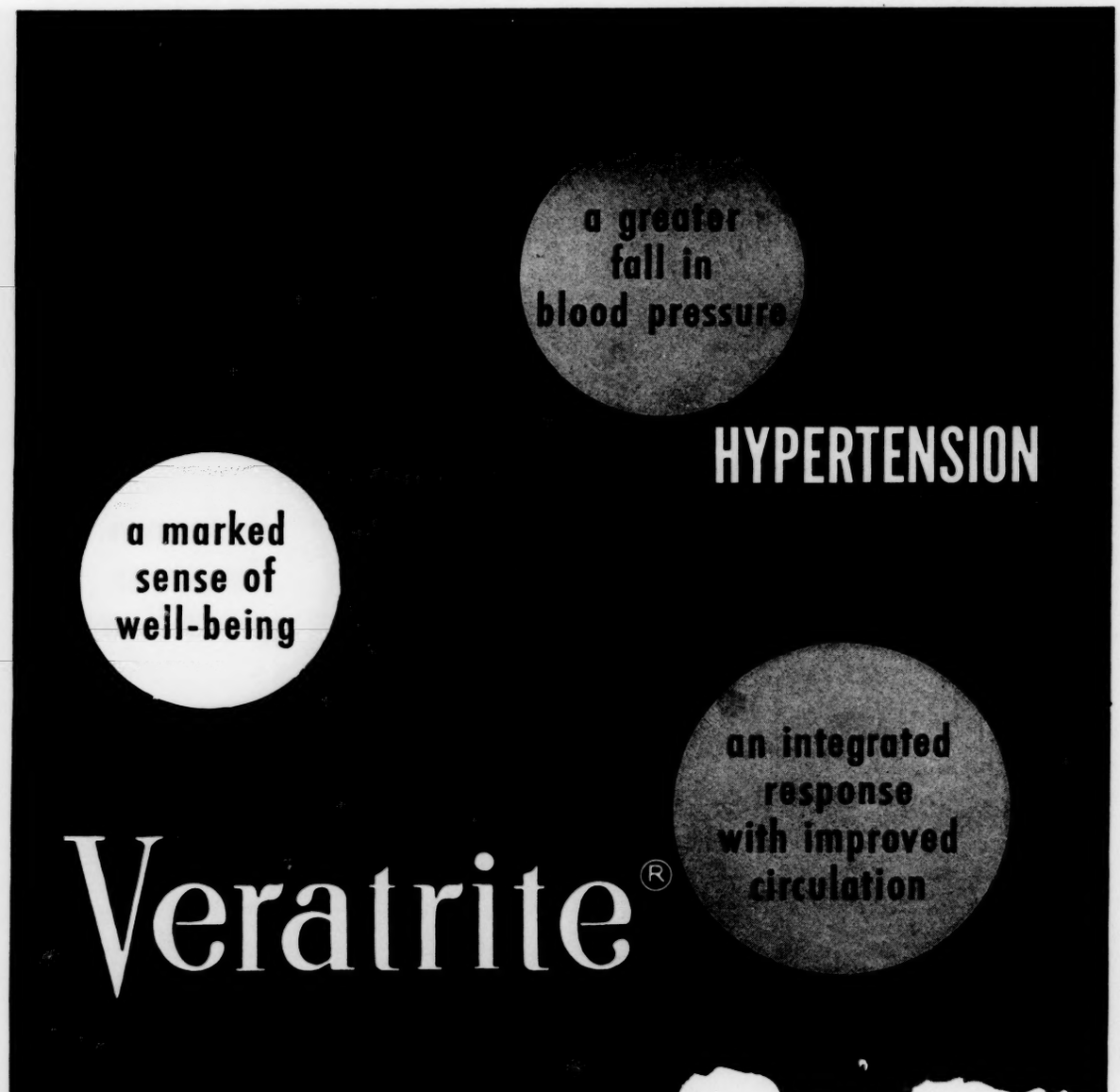

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1. Walker, W.J.: Obesity as a Problem in Preventive Medicine, U.S. Armed Forces M.J. 1:393, 1950.

2. John, H.J.: Dietary Invalidism, Ann. Int. Med. 32:595, 1950.

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The American Journal of Medicine

VOL. IX JULY, 1950 No. 1

Editorial

A New Era in Medical Research and Practice

MEDICAL historians of the future will probably mark the year 1949 as the beginning of a new era in medical research and practice, citing as the precipitating document the report of Hench, Kendall, Slocumb and Polley[1] on the effects of cortisone in the treatment of rheumatoid arthritis. The full significance of this event will not be apparent for many years to come, nor can we as yet evaluate the results definitively in terms of known principles. Nevertheless, we can already speculate on the broad effects in basic and clinical research.

The so-called degenerative diseases today account for the major share of mortality and morbidity in industrially developed areas of the world. Obscure in origin and resistant to treatment, these diseases have challenged the best thought in research and medicine for several generations. Although there has been individual speculation as to inter-relationships, there had not been until this year convincing evidence to provide medical scientists with a clue to a common factor in the etiology of such diverse conditions as rheumatoid arthritis, status asthmaticus, glomerular nephritis and lymphatic leukemia.

Recent studies have given the medical world evidence that the adrenal steroid, cortisone, produces positive therapeutic effects in diseases not previously known to be associated with hormonal imbalance. The direct result has been to provide a promising therapeutic approach through adrenocortical research. By the close of 1949 scientists in various parts of the United States had begun clinical testing of cortisone and pituitary adrenocorticotropic hormone in no less than fifty disease entities. As might have been expected the results in many cases were negative; in others, inconclusive, and in a few, dramatically encouraging. Studies also had been launched to determine the physiologic properties of both cortisone and ACTH.

Work had begun on the formidable problems of producing the hormone in sufficient quantities, first to supply it for expanded scientific study of its clinical usefulness and eventually to satisfy the demands of physicians and their arthritic patients. As these technical problems are solved, other difficulties in the field of health economics undoubtedly will arise. The cost and distribution of cortisone and ACTH will present problems. These, too, must be solved if adequate research is to be done and if the substances are ultimately to be used widely for the benefit of mankind.

The contribution of Hench, Kendall and their co-workers will, in fact, have its most powerful effects in fundamental research. Their work presents the medical scientists with a clue to systematic study of the relation of hormones to chronic disease. As scientists of the past epoch sought to find specific causes through bacteriology, so in the new era investigators may seek for a

[1] *Proc. Staff Meet., Mayo Clin.*, 24: 181, 1949.

metabolic factor as a common denominator underlying many baffling diseases.

Endocrinology, physiology and biochemistry probably will take the dominant position which bacteriology and its related disciplines have held in medical research for three-quarters of a century. The synthesis of newly discovered substances also is a possibility which promises a new era in chemotherapy, following its recent triumphs in the protozoal and bacterial diseases.

Certainly, the isolation and synthesis of cortisone and the demonstration of its therapeutic effects point the way to a great expansion of research upon the steroid hormones. Intensive study of steroid metabolism may uncover basic mechanisms that account for the difference between health and disease. A common factor in the metabolic process, for example, may be responsible for maintaining normal functions in various organs not previously believed to be related, or some one series of chemical reactions may be found to be essential for maintaining many substances normally present in the body. Much fundamental study must be done before such conclusions can be reached.

In any event, the achievements of hormonal research in 1949 open many new fields for intensive investigation. Study of the patterns of urinary steroid excretion and isolation of new substances secreted by the endocrine glands are only two lines of investigation suggested by recent developments. New methods of testing for biochemical deficiencies also are needed. Because the new leads are promising, more scientists will be attracted to the basic study of disease and to the search for a common cause, as contrasted with the former emphasis upon specific etiology and localized diseases.

Research and scientific medicine have been moving slowly toward a new theoretic and clinical synthesis. With the advance of biochemistry and biophysics there have been vast improvements in the methods, measurements and instruments available to the medical investigator. Without these tools the closer integration of the disciplines, which brought about the accomplishments of 1949, could not have been achieved. In the meantime, however, scientists in general and the public have placed major emphasis upon the search for specific causes or cures of specific diseases.

Until now it has been difficult to convince the supporters of medical research that basic study could yield far-reaching results, not only in a single disease such as rheumatoid arthritis, but in a variety of conditions which affect a large proportion of the world's population. One of the most significant results of the introduction of cortisone assuredly will be increased support of basic research, as the indispensable foundation for progress in both the physical and mental diseases of mankind.

LEONARD A. SCHEELE, M.D.,
Surgeon General
United States Public Health Service,
Federal Security Agency

Clinical Studies

Further Clinical and Experimental Studies on the Pathogenesis of Cushing's Syndrome*

PETER HEINBECKER, M.D.† *and* MATHER PFEIFFENBERGER, JR., M.D.
St. Louis, Missouri

In previous publications[1,2] a tumor of the adrenal cortex, a tumor of the thymus, a tumor of the ovary or atrophic changes in the paired paraventricular nuclei of the hypothalamus were listed as possible primary causes of Cushing's syndrome. It was proposed that any of these primary causes could effect similar changes in the glandular hypophysis. One of these alterations is overaction of the eosinophile cells with or without cytologic preponderance. Another change is degranulation with or without hyalinization of the basophile cells. The mechanism by which the hyalinization of the basophile cells (i.e., Crooke cells) is brought about remained unsettled. Experimental evidence has since been secured to demonstrate the mechanism responsible for this change. Additional studies of glandular interrelationships have been made which indicate that an actively secreting thymic tumor probably cannot, as previously supposed, be a primary cause of Cushing's syndrome.

Experimental evidence has been secured in the dog that complete denervation of the neural hypophysis or the interruption of afferent nerve pathways to the supraoptic and paraventricular hypothalamic nuclei results in functional and pathologic changes in the body similar to those exhibited by persons with Cushing's syndrome.

Two additional cases of Cushing's syndrome are herein presented which exhibited typical clinical and pathologic findings. In one of these cases the primary lesion was an atrophy of the paraventricular hypothalamic nuclei; and in the other the primary lesion was an adrenal cortical tumor. The demonstration again that a lesion primary either in the hypothalamus or in a peripheral endocrine gland can produce similar changes in the body as a whole is deemed significant because evidence is becoming available that such a dual origin is possible for many major endocrine disorders. Thus it has been shown that overaction of the supraoptic and paraventricular nuclei could effect changes in the glandular hypophysis which are responsible for the development of hyperthyroidism of the exophthalmic type.[3] Hyperthyroidism without exophthalmos may arise also from an adenomatous change primary in the thyroid gland itself. Diabetes mellitus may arise from changes primary in the hypothalamus or in the pancreas.

When the lesion is primary in the hypothalamus, constitutional organ or tissue susceptibility to endocrine influences as well as variations in the magnitude of such influences appear to determine whether the end effect will be a single disease process or a number of them as in Cushing's syndrome.

CASE REPORTS

CASE 1. A married white female, age fifty-eight, entered Barnes Hospital on June 17, 1947, because of shortness of breath and left chest pain of two months' duration. Death resulted three weeks later from cardiac failure.

The past history revealed that the patient was married at the age of nineteen; her weight at that time was 130 pounds. Following her first

* From the Department of Surgery, Washington University School of Medicine, St. Louis, Missouri.
† Recipient of grants-in-aid of research from the Commonwealth Fund and the United States Public Health Service.

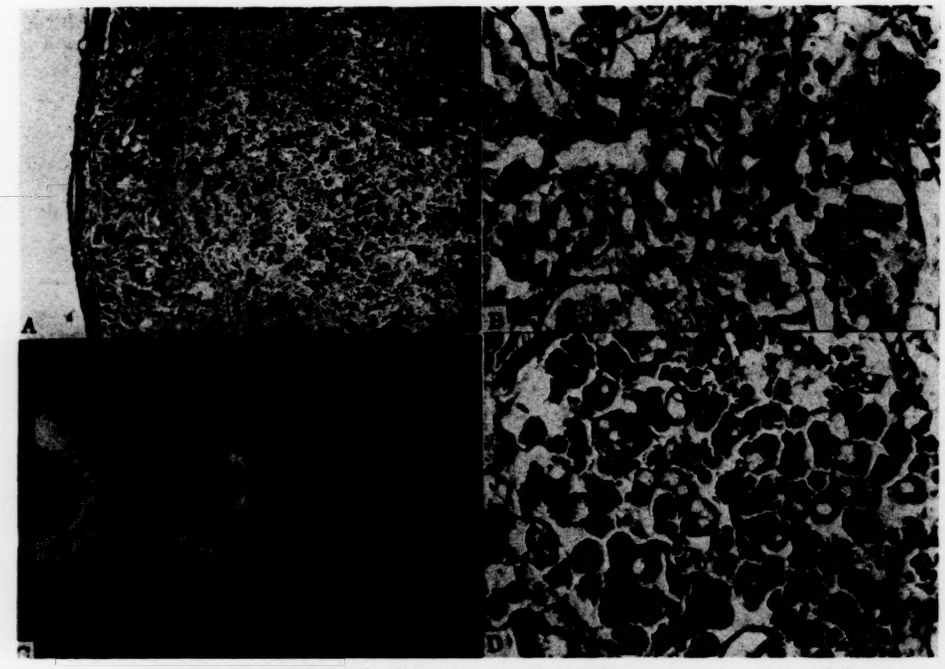

FIG. 1. A, photomicrograph (× 45) of the adrenal gland, Case I, showing most of the cortex replaced by carcinomatous tissue with a small amount of normal adrenal cortex remaining; B, photomicrograph (× 510) of the glandular hypophysis, Case I, showing several large basophiles which exhibit degranulation, hyalinization and vacuolization of their cytoplasm; C, photograph (× 3) of the base of the brain in the region of the hypothalamus and optic chiasm, Case II. Note the marked bulging of the dilated third ventricle which has pushed the optic chiasm forward. D, photomicrograph (× 510) of the glandular hypophysis, Case II, showing many degranulated, hyalinized and vacuolated basophiles.

pregnancy thirty-eight years previously she gained weight rapidly and reached 300 pounds. She had six more children over the ensuing fifteen years. Her weight averaged 300 pounds for years. During the year prior to her hospital admission she lost 100 pounds without dieting; in this interval she experienced weakness and fatigue. During the seven years prior to her admission she developed increasing plethora and fullness of the face. She was known to have had high blood pressure for five years. Four years before admission she was discovered to have diabetes mellitus; 20 units of regular insulin daily were required to control her diabetes. During this period she had nocturia, polyuria, polydipsia and polyphagia. Her water intake at times reached fifteen to twenty glasses per day.

Physical examination on admission showed a plethoric, somewhat cyanosed facies. Moderate obesity of buffalo type distribution was present. Hairiness of the face, arms and legs was quite marked. The clitoris was not enlarged. The heart definitely was enlarged. Arteriosclerosis of the retinal arteries was definite. Blood pressure was 220/130.

Laboratory findings were as follows: red blood cells 4.89; hemoglobin 12.5 gm. per cent; white blood cells 7,950; differential-basophiles 0; eosinophiles 2; stab forms 14; juveniles 4; segmented forms 54; lymphocytes 23; monocytes 3 per cent. Kahn test was negative. Urine showed sugar 1+. Fasting blood sugar 237 mg. per cent; sugar tolerance curve definitely diabetic; non-protein nitrogen 21 mg. per cent; total plasma protein 6.0 gm. per cent with albumin 3.4 gm. per cent and globulin 2.6 gm. per cent; serum calcium 11.3 mg. per cent; phosphorus 5.6 mg. per cent; alkaline phosphatase 8 Bodansky units; plasma sodium 144.9 mEq./L.; cholesterol 152 mg. per cent; P.S.P. test 45 per cent excretion of the dye in two hours. X-ray examination of the skeleton showed generalized osteoporosis of the spine and hyperostosis frontalis interna.

A complete autopsy was obtained. It revealed carcinoma of the adrenal cortex, bilateral. (Fig. 1A.) There were also areas of focal hyperplasia of the adrenal cortex. Metastatic carcinoma was evident in the portahepatic, peripancreatic and tracheobronchial lymph nodes,

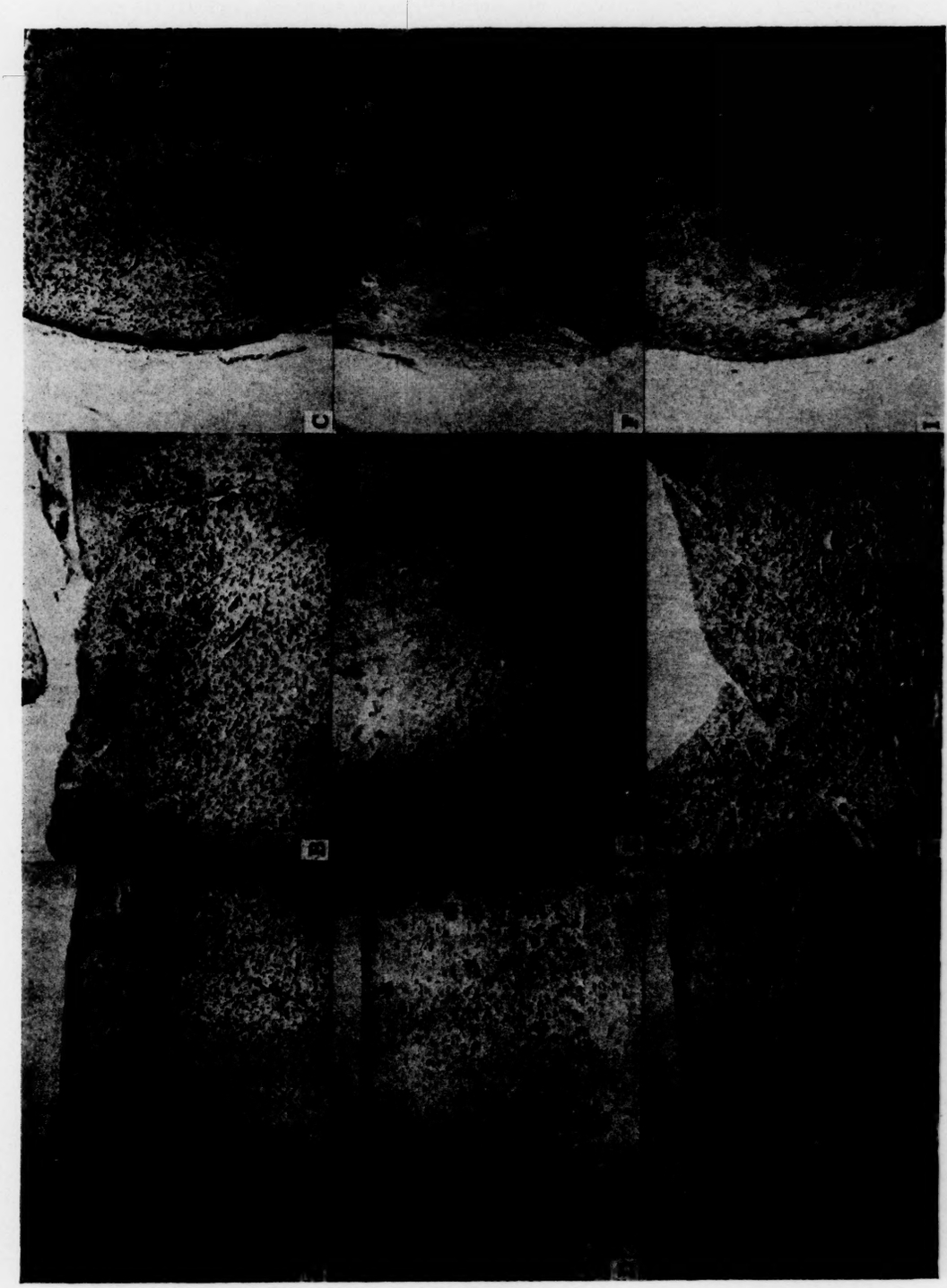

FIG. 2. Photomicrographs (× 45) of the hypothalamic paraventricular, supraoptic and mammillary nuclei in a normal human control, Cases I and II. A, paraventricular nucleus, normal human control, showing number and distribution of cells; B, supraoptic nucleus, normal human control, showing number and distribution of cells; C, mammillary nucleus, normal human control, showing number and distribution of cells; D, paraventricular nucleus, Case I, showing normal appearance (compare with A); E, supraoptic nucleus, Case I, showing normal appearance (compare with B); F, mammillary nucleus, Case I, showing normal appearance (compare with C); G, paraventricular nucleus, Case II, showing marked loss of cells (compare with A). Note thinning of the ependymal lining of the third ventricle. H, supraoptic nucleus, Case II, showing normal appearance (compare with B); I, mammillary nucleus, Case II, showing normal appearance (compare with C).

in the bone marrow and in the liver. Hyalinization of the islets of Langerhans was present. Arteriolar nephrosclerosis was slight. The kidney on the right weighed 220 gm. and on the left 250 gm. (normal 150 gm.). Hypertrophy and dilation of the heart were present; it weighed 420 gm. (normal in female 250 gm.). Arteriosclerosis of the aorta and the coronary arteries was moderate in degree. Nodular cirrhosis of the liver with fatty metamorphosis was present. There was cholesterolosis of the gallbladder.

Serial sections of the hypophysis stained differentially according to the method of Rasmussen (personal communication) showed normal eosinophile and chromophobe cells. There were many hyalinized basophile cells. (Fig. 1B.) Serial sections of the hypothalamus showed normal supraoptic, paraventricular and mammillary nuclei. (Fig. 2D, E and F.) There was no enlargement of the cerebral ventricles.

Case II. A married white male, age fifty-nine, was admitted to Barnes Hospital on October 16, 1941, for treatment of cardiac failure of seven months' duration. Physical examination at that time revealed an obese, florid individual who appeared chronically ill. He showed mental dullness and confusion. A coarse tremor of his right hand and a hyperactive right knee jerk were present. Blood pressure was 145/80.

Laboratory findings were as follows: red blood cells 3.46; hemoglobin 11.3 gm. per cent; white blood cells, 8,900; differential—basophiles 1; eosinophiles 0; stab forms 8; segmented forms 76; lymphocytes 12; monocytes 3 per cent. Kahn test was negative. Urine showed 4+ sugar repeatedly. Total plasma proteins 4.6 gm. per cent with albumin 3.4 gm. per cent and globulin 1.2 gm. per cent. Plasma chlorides 515 mg. per cent; non-protein nitrogen 22 mg. per cent; fasting blood sugar 78 mg. per cent; blood cholesterol 225 mg. per cent; B.M.R. −20.

The patient remained in the hospital for one and one-half months during which time he developed a high blood sugar of 211 mg. per cent; other significant laboratory findings were blood calcium 7.7 mg. per cent; phosphorus 1.9 mg. per cent; alkaline phosphatase 3 Bodansky units. Ventriculograms revealed evidence of slight to moderate dilation of the lateral ventricles and some cortical atrophy. The patient was sent home after his general condition improved.

During the next seven years he was cared for at home. He remained mentally dull and unresponsive. Purplish striae appeared on his thighs and chest. Purpuric ecchymoses developed on his upper extremities. In 1942 he began to develop polyuria, polydipsia and polyphagia. He became moderately obese with fat distribution of the buffalo type. Diastolic hypertension was first noted in 1944. Mental instability increased. His diabetes mellitus varied in severity. Usually 20 units of regular insulin daily were required to control his diabetes but for one five-month period in 1944 no insulin was required. In the four years preceding his death his hypertension, cardiorenal disease and diabetes mellitus became progressively worse. Osteoporosis of the spine was definite. He became subject to increasing degrees of headache and vomiting. He died at home on February 18, 1948. The clinical diagnosis was Cushing's syndrome.

At autopsy a definite internal hydrocephalus was present with considerable atrophy of the cerebral convolutions. This involved the third ventricle resulting in a thinning of its floor. The dilated third ventricle pushed the optic nerves forward. (Fig. 1C.) The median eminence was also markedly thinned as a result of the ventricular dilation. An area of softening in the left frontal lobe was present. There were hypertrophy and dilation of the heart which weighed 660 gm. (normal in male 300 gm.). The liver showed fatty infiltration. The right adrenal weighed 12 gm. and the left adrenal 10.5 gm. (normal adult 5–6 gm.). Microscopic examination revealed this enlargement of the adrenals to be due to hyperplasia without any evidence of carcinoma. The pancreas was infiltrated with fat. The right kidney weighed 92 gm. and the left 102 gm.; there was thickening of the interlobular arteries. The parathyroid glands were enlarged, two of them weighing 500 mg. together (average for the adult 35 mg. each). The right testis was atrophic, weighing only 7.5 gm.; the left testis weighed 13 gm. (normal adult testis and epididymis 20–27 gm.). The whole pituitary gland weighed 600 mg. (normal 610 mg.). Generalized arteriosclerosis of moderate degree was present. The arteriosclerotic vessels showed fragmentation of the elastic tissue in the walls of the arterioles with the infiltration of calcium salts.

Serial sections of the pituitary gland showed the eosinophile and chromophobe cells to be normal. The basophile cells showed considerable hyalinization. (Fig. 1D.) Serial sections of the hypothalamus showed marked atrophy of the cells of the paraventricular nuclei. (Fig. 2G.) It

was estimated that not more than 10 to 15 per cent of the normal cell content was present. The supraoptic nuclei showed slight if any cell loss. (Fig. 2H.) The mammillary nuclei appeared normal. (Fig. 2I.)

Two cases of Cushing's syndrome with different primary lesions are presented. Previously[1] four other cases of Cushing's syndrome were described in which histologic studies of the hypothalamus indicated a primary lesion of the hypothalamic nuclei, particularly the paraventricular. One case was also cited in which a benign tumor at the foramen magnum causing increased intraventricular pressure had led to the development of Cushing's syndrome; in that case operative removal of the tumor was followed by regression of the signs and symptoms of Cushing's syndrome. That patient is still alive without recurrence of her symptoms. Two cases of Cushing's syndrome due to primary carcinoma of the adrenal cortex were also described. Since this previous report of seven cases of Cushing's syndrome three cases other than those reported herein have been observed. In all three the spinal fluid pressure measured between 230 and 240 mm. water. Two of these had a laparotomy with exposure of the adrenal glands and the ovaries. No tumor was found in either patient. In the third patient no evidence of an adrenal tumor was found clinically. It is assumed that two of these patients developed Cushing's syndrome because of a primary depression of the paraventricular hypothalamic nuclei and the third probably did so also. The cause of the increased intraventricular pressure is not known. It is suggested that there exists in such persons a local susceptibility of the blood vessels of the choroid plexus to the vasoconstricting hormones released as a result of functional depression of the hypothalamic nuclei which innervate the neural hypophysis. Such vasoconstriction might either increase the amount of cerebrospinal fluid formed, interfere with its absorption, or both.

HORMONAL MECHANISMS INVOLVED IN CUSHING'S SYNDROME

An analysis of the mechanism responsible for the production of the signs and symptoms of Cushing's syndrome reveals the widespread influence of the overaction of

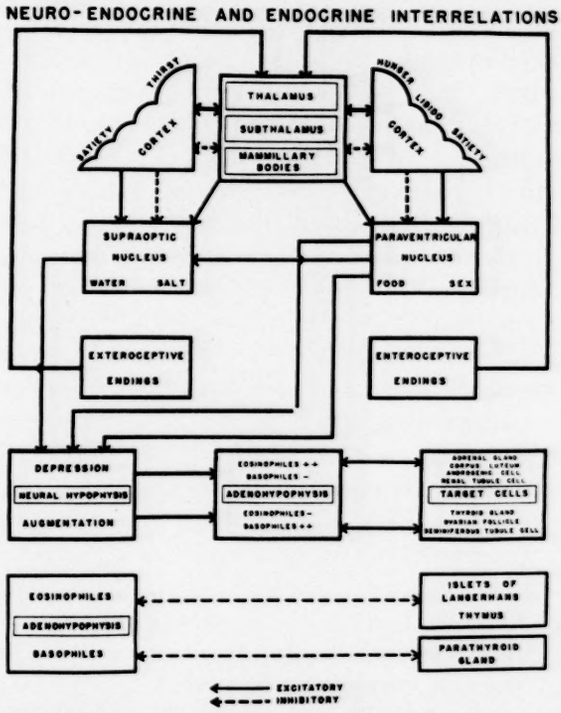

FIG. 3. Diagram to show manner in which influences from the central nervous system, acting through the hypothalamus on the neural hypophysis, can effect changes in the endocrine glands.

the hypophysial eosinophile-adrenal cortical hormone complex with underaction of the hypophysial basophile-thyroid hormone complex. Figure 3 is a diagram indicating the possible neuro-endocrine and inter-endocrine mechanisms for the maintenance of homeostatic endocrine interrelations and the means by which endocrine imbalances toward the hypophysial eosinophile or basophile side may occur. The significance of an endocrine imbalance in favor of the eosinophile side is shown most completely in the development of Cushing's syndrome while an imbalance in favor of the basophile side is best exhibited by hyperthyroidism with exophthalmos.

Experimentally one method of initiating a glandular imbalance in favor of the hypo-

physial eosinophile-adrenal cortical hormone complex is to produce a loss of or a decrease in those factors in the neural hypophysial secretion which are under the trophic influence of nerve fibers from the paired paraventricular nuclei. This may be accomplished either by interruption of the afferent fibers to the paired paraventricular nuclei or by severance of the fibers issuing from these nuclei to innervate the neural hypophysis. Both procedures effect a depression of the normal activity of the paired paraventricular nuclei and consequently a depression of those neural hypophysial hormone factors to which the paraventricular nuclei are trophic. Our experimental evidence indicates that normally a balanced antagonistic relationship exists between the hormone factors secreted by the inner two zones of the adrenal cortex and those neural hypophysial secretions to which the paraventricular nuclei are trophic. A change in the amount of these neural hypophysial hormone factors modifies particularly the metabolism of carbohydrate, protein and fat and the development and activity of the sex glands. With a decrease in the amount of these neural hypophysial hormone factors this modification is effected through an increased release of the hormone factors secreted by the inner two zones of the adrenal cortex. Recent clinical observations[4] on the effect of ACTH and compound E indicate that these same neural hypophysial hormone factors also have some direct or indirect influence on salt and water balance. Our experimental evidence also indicates that those neural hypophysial hormone factors which are under the trophic influence of fibers from the paired supraoptic nuclei are entirely concerned with modification of the salt and water balance of body tissues. The secretion of the glomerular zone of the adrenal cortex, desoxycorticosterone or some similar steroid hormone, is in balanced antagonistic relation with the antidiuretic principle of the neural hypophysial secretion.[5]

In experimental dogs loss or depression of those neural hypophysial hormone factors to which the paraventricular nuclei are trophic results in an initial loss of basophile cells in the glandular hypophysis; ultimately, the basophile cells return in a degranulated or hyalinized form and are functionally ineffective. On the other hand, in normal dogs an excess of neural hypophysial hormone (i.e., prolonged administration of exogenous whole posterior pituitary extract) results in an increase in the number of highly granular basophiles in the glandular hypophysis. Clinically these experimental conditions are simulated in the first instance in Cushing's syndrome due to a primary atrophy of the paired paraventricular nuclei and in the latter instance in hyperthyroidism with exophthalmos which is considered to be due to a primary overactivity of the paired paraventricular nuclei.[3]

As stated previously, in our experimental dogs the loss or depression of those neural hypophysial hormone factors to which the paraventricular nuclei are trophic increases the activity of the hormone factors secreted by the inner two zones of the adrenal cortex. This increased activity is probably due to both increased effectiveness and increased secretion of these adrenal cortical hormone factors. In such dogs the increased effectiveness is brought about by a loss or depression of the normally antagonistic neural hypophysial hormone factors. The increased effectiveness of these adrenal cortical hormone factors causes an increased stimulation of hypophysial eosinophile activity. The latter, in turn, effects a stimulation of the inner two zones of the adrenal cortex leading to hyperplasia and an actual increased release of adrenal cortical hormone factors. Therefore, loss or depression of those neural hypophysial hormone factors to which the paraventricular nuclei are trophic results in a self-augmenting cycle which causes persistent overactivity of the hypophysial eosinophile-adrenal cortical hormone complex. In cases of Cushing's syndrome due to an adrenal cortical tumor the excess of adrenal hormone factors secreted by the tumor stimulates directly hypophysial eo-

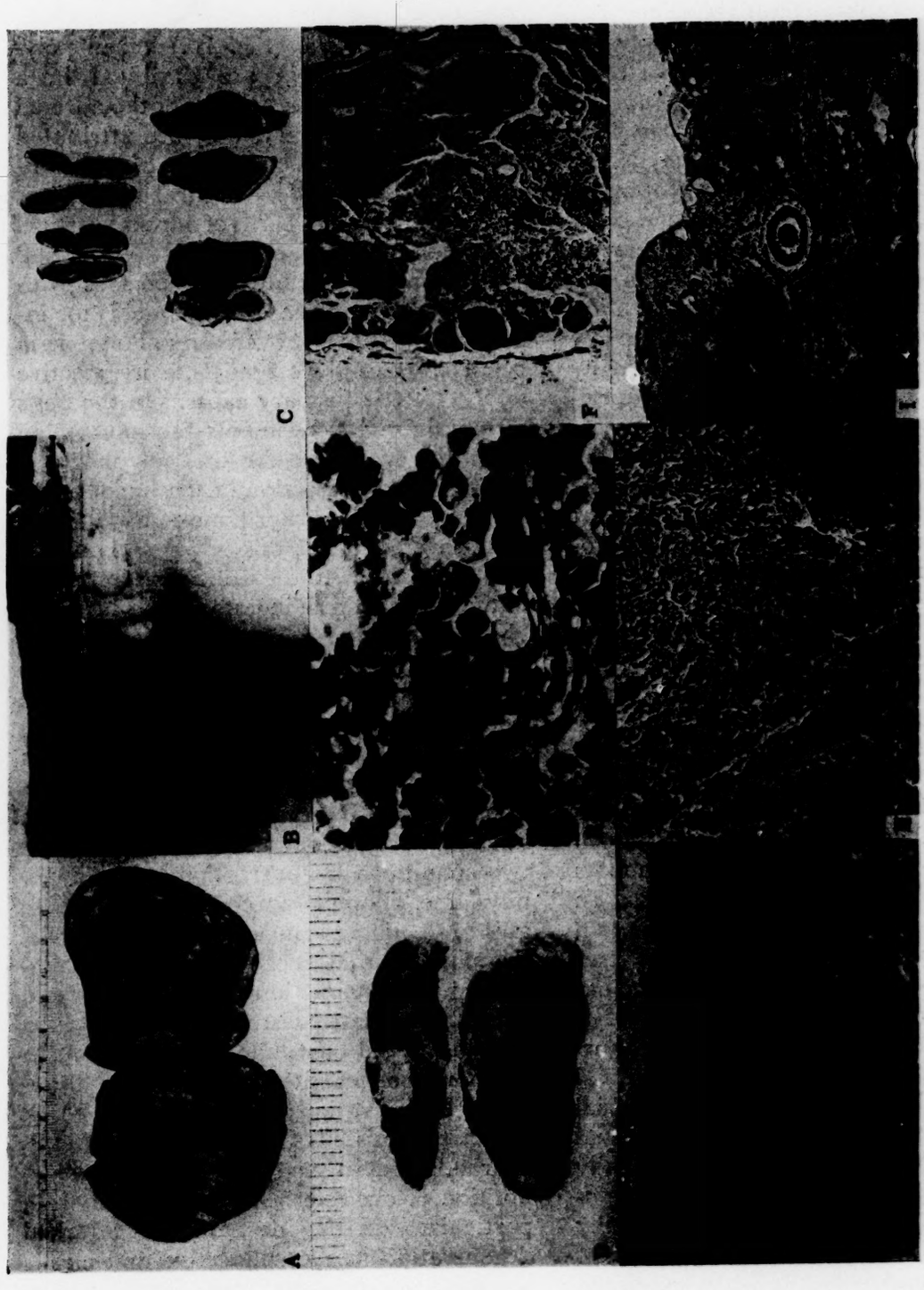

FIG. 4. A, photograph (× ⅝) of the heart, dog PIB. Heart is enlarged and ventricular walls are thickened. Note the marked concentric hypertrophy of the left ventricle; B, photograph (× 5) of the intimal surface of the upper portion of the descending thoracic aorta, dog PIB, it shows several prominent plaques. Micro-incineration studies revealed evidence of calcium deposition beneath these lipoid-containing plaques. C, photograph (× ⅝) of the adrenal glands of dog PIB (bottom) and of a normal dog of comparable size (top). Note the marked hypertrophy of the inner two zones of the cortex, dog PIB. D, photograph (× 2½) of the thyroid and parathyroid glands of dog PIB (top) and of a normal dog of comparable size (bottom). Note the marked hypertrophy of the parathyroid gland and the marked atrophy of the thyroid gland, dog PIB, when compared with the normal control. (Divisions of the scale at top of photomicrograph are 1 mm.) E, photomicrograph (× 510) of the glandular hypophysis, dog PIB, showing many enlarged basophiles exhibiting prominent degranulation, hyalinization and vacuolization; F, photomicrograph (× 45) of the thyroid gland, dog PIB, showing marked atrophy of the thyroid acini. A few acini distended with colloid remain at the periphery of the gland; G, photomicrograph (× 45) of the adrenal cortex, dog PIB. Note the normal glomerular zone, the markedly hypertrophied fascicular zone and the moderately hypertrophied reticular zone; H, photomicrograph (× 45) of the parathyroid gland, dog PIB. Hypertrophy is due to the increased numbers of principal cells, normal in appearance. I, photomicrograph (× 45) of the markedly atrophic ovary, dog PIB. One atretic follicle can be seen. The remaining follicles are completely atretic or cystic.

sinophile activity and partially or completely neutralizes those neural hypophysial hormone factors to which the paraventricular nuclei are trophic. Thus the same persistent overactivity of the hypophysial eosinophile-adrenal cortical hormone complex results.

In our experimental dogs with complete denervation of the neural hypophysis the increased effectiveness of the hypophysial eosinophile-adrenal cortical hormone complex is evidenced by the marked decrease in circulating lymphocytes.[6] Clinical corroboration of this experimental observation has been found by us and others[7] in the low circulating lymphocyte levels exhibited by patients with Cushing's syndrome. Experimental evidence presented elsewhere[8] indicates that renal blood flow is under the direct influence of hypophysial eosinophile activity. It has been shown by us that adrenal cortical extract does not significantly alter renal blood flow in normal, in simply hypophysectomized and in totally hypophysectomized dogs. However, it produces an appreciable increase of renal blood flow in dogs with complete denervation of the neural hypophysis; this must be due to a direct stimulation of hypophysial eosinophile activity.[9] The following clinical observation affords positive evidence that a stimulation of hypophysial eosinophile cell activity may be caused by increased amounts of adrenal cortical hormone factors: In children with Cushing's syndrome due to a primary adrenal cortical tumor there is at first skeletal overgrowth followed by premature closure of the bony epiphyses. It is accepted generally that the growth hormone factor is secreted by the hypophysial eosinophile cells. Evidence that hypophysial eosinophile overactivity leads to adrenal cortical hyperplasia is found experimentally in our dogs following complete neural hypophysial denervation (Fig. 4c) and clinically in all cases of Cushing's syndrome.

Polydipsia and polyuria when exhibited by persons with Cushing's syndrome due to a lesion primary in the hypothalamus are attributed to depression of the paired supraoptic nuclei which may or may not be recognizable histologically. These functional and histologic changes are the result of increased pressure on the nuclei adjoining the third ventricle. (Fig. 1c.) When polydipsia and polyuria are exhibited in a person with a primary tumor of the adrenal cortex or of the ovary, they are attributed essentially to a neutralization of the antidiuretic hormone of the neural hypophysis by the increased amounts of adrenal cortical hormone[5] or of progesterone.[10]

The obesity exhibited by persons with Cushing's syndrome is attributed to increased appetite and overeating. Polyphagia occurs in Cushing's syndrome irrespective of the latter's primary cause. On the basis of our animal experiments the increase in appetite responsible for the polyphagia is attributed to overaction of the hypophysial eosinophile-adrenal hormone complex.[11] Because overaction of this hormone complex also interferes with the utilization in muscle of the carbohydrate ingested[12] and increases gluconeogenesis from protein,[13] it presumably may provide additional carbohydrate for conversion into fat which then may be stored.

Arteriosclerosis is a constant development in persons exhibiting Cushing's syndrome. It occurs also in early life in humans with renal dwarfism. Common findings in these two conditions are overaction of the hypophysial eosinophile-adrenal cortical mechanism, a depression of the hypophysial basophile-thyroid mechanism, and hypertrophy with overaction of the parathyroid glands.[14] The latter disturbance is attributed to hypophysial basophile cell depression.[3]

Another effect of the above hormonal imbalances is elevation of the blood cholesterol. Arteriosclerosis in Cushing's syndrome is characterized in part by an increased deposition of cholesterol in the arterial wall, particularly in the intimal layer. Marked degeneration in the connective and elastic tissue of the skin and of other tissues including the muscle layers of the arterial wall has been found in Cushing's syndrome.[1] Overaction of the parathyroid glands (pre-

sumably due to their enlargement with cytologically active cells) is considered responsible for the demineralization of bone which occurs in both Cushing's syndrome and renal dwarfism. It is suggested that the calcium salt depleted from the bones is available for deposition in the degenerated elastic fibers. These fibers have been shown by Lansing et al.[15] to be the ones in which calcium salts are deposited in arteriosclerosis.

In persons with Cushing's syndrome due to primary atrophy of the paired paraventricular nuclei with or without atrophy of the supraoptic nuclei, diastolic hypertension is regarded as a response to the resultant overaction of the hypophysial eosinophile-adrenal-renin hormone complex, just as it is in the puncture type dogs herein reported. Depression of the secretion of the neural hypophysis, either by denervation of the entire neural hypophysis or by the interruption of nerve pathways excitatory to the hypothalamic nuclei, results in an overaction of the glandular hypophysial eosinophile cells. Diabetes insipidus also results when the entire neural hypophysis is denervated but not when only the nerve pathways excitatory to the hypothalamic nuclei are interrupted. Since hypertension develops under both circumstances, it apparently is not the loss of the antidiuretic fraction of the posterior lobe hormone which is the essential factor in the development of the endocrine imbalance.

In other experiments[9] it has been shown that the hypophysial eosinophile cells are trophic to the renal tubule cells. This trophism may express itself in a stimulation of the renal tubule cells to augment the excretion of diodrast or sodium para-amino hippurate. Diodrast Tm excretion was elevated above the average normal in all of the four puncture dogs reported in this presentation. This is interpreted as an effect of the overaction of a renotrophic hormone produced by the hypophysial eosinophile cells. Renin when released from renal tubules in turn stimulates hypophysial eosinophile cell maturation.[10] Such eosinophile cell preponderance with overaction has been produced experimentally in the dog by wrapping one kidney in silk with or without the removal of the other kidney. It has been shown by us that the hypertension which follows the wrapping of one kidney subsides after enlargement of the remaining unwrapped kidney is adequate to re-establish normal renal tubular function.[10] With adequate enlargement of the unwrapped kidney and the return of blood pressure to normal the cytology of the glandular hypophysis returns to normal.

Another possible mechanism for the release of renin is the action of the vasomotor nerves in effecting constriction of the skin and visceral blood vessels including those to the kidney. The effect of the sympathetic nerves in releasing epinephrine from the adrenal medulla forms the humoral component of the emergency neurohumoral mechanism for the control of the caliber of the blood vessels. Narrowing of the main renal vessels or of the internal arterioles of the kidney releases renin. It has been shown also that epinephrine augments the amount of adrenal cortical hormone released.[16] As previously stated, the latter hormone is trophic to the maturation of the hypophysial eosinophile cells which in turn secrete a renotrophic hormone.

It is certain, too, that with the development of arteriosclerosis in the arterioles of the body, including those of the kidney, renin release would be augmented as part of the adaptation response of the body to maintain adequate kidney function.

In the diastolic hypertension of Cushing's syndrome, as in all other forms of diastolic hypertension, a mechanism exists for stimulation of the heart, thereby maintaining the elevated blood pressure caused by constriction of the arterioles of the body generally. The agents which can exercise such an influence on the heart are angiotonin,[17] the anterior pituitary hormone[18] and epinephrine.[19] Adrenal cortical hormone is essential for this action of angiotonin, anterior pituitary hormone and epinephrine; but overaction of the adrenal cortical hormone in itself does not increase renal blood flow[9]

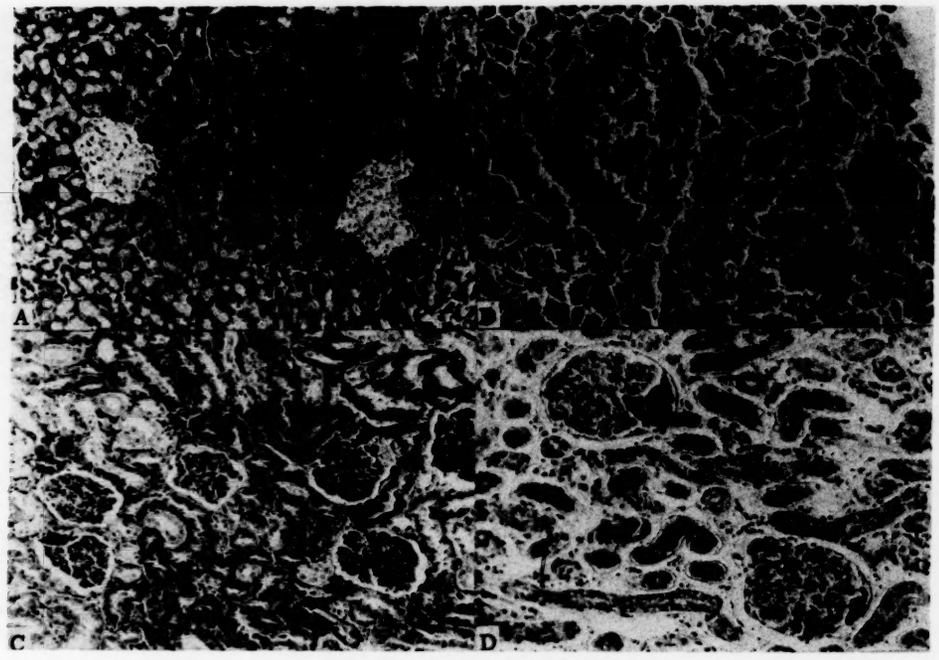

FIG. 5. A, photomicrograph (× 135) of the pancreas, dog PIB (biopsy specimen taken three years after puncture type I operation); B, photomicrograph (× 135) of the pancreas, dog PIB (autopsy specimen seven and one-half years after puncture type I operation). Note the normal acinar tissue but the marked atrophy of the islets of Langerhans with striking loss of cellular components (compare with A). This change was present throughout all regions of the pancreas; C, photomicrograph (× 135) of the renal cortex of a normal dog of the same size as dog PIB; D, photomicrograph (× 135) of the renal cortex of dog PIB. Note the marked hypertrophy of the glomeruli and tubules (compare with C).

and by inference would not increase cardiac output over the normal.

It has been reported previously[10] that when the amount or effectiveness of the neural hypophysial hormone is diminished, the blood vessels of the body are rendered more responsive to the vasoconstricting action of epinephrine, desoxycorticosterone and renin. This sensitization of the blood vessels to vasoconstricting agents can be assumed to play a role in Cushing's syndrome in which the posterior lobe hormone is decreased or neutralized.

Obesity, which is recognized as an associated or contributory factor in the pathogenesis of diabetes mellitus in man[20,21] is found constantly in Cushing's syndrome. Experimental evidence has previously been offered attributing such obesity to overaction of the hypophysial eosinophile-adrenal hormone complex.[11] As stated before, overaction of this hormone complex has been shown by Colowick, Cori and Slein[12] to inhibit the utilization of carbohydrate by body tissues. Release of this inhibition is effected by insulin. In Cushing's syndrome insulin sensitivity is depressed. The mechanism of this decreased insulin sensitivity is attributed also to overaction of the eosinophile-adrenal hormone complex.[22] In addition such overaction has been shown to depress the islets of Langerhans to a degree which is recognizable histologically. (Fig. 5B.) In dogs functional depression of the islets by the administration of anterior pituitary hormone has been shown previously by Young,[23] Campbell and Best[24] and others. In acute experiments Ham and Haist[25] have offered evidence of histologically demonstrable depression of the beta cells of the islets following the administration of anterior pituitary extracts.

On the above evidence it is postulated that diabetes mellitus (whenever a primary lesion of the pancreas can be excluded) may be caused by influences primary in the central nervous system of a type which depress the paired paraventricular hypo-

thalamic nuclei. These influences presumably effect only functional changes in the hypothalamic nuclei at first. Later the cells of the paraventricular nuclei may show actual histologic changes as demonstrated by Morgan et al.[26] It is interesting to speculate as to whether or not the constitutional susceptibility of persons developing diabetes mellitus may consist in part of a susceptibility of the cells of their paraventricular nuclei to succumb earlier to atrophy from neurogenic depression than the cells of persons who do not develop diabetes mellitus. In those cases of Cushing's syndrome due to a primary tumor of the adrenal cortex there also results overaction of the hypophysial eosinophile hormone complex; the two mechanisms by which the excess adrenal cortical hormones stimulate this complex to overaction have been previously explained. Consequently, the mechanism for the pathogenesis of diabetes mellitus in such cases is considered similar to that which pertains when the primary cause of Cushing's syndrome is a depression of the hypothalamic paraventricular nuclei.

Osteoporosis is found almost invariably in persons exhibiting Cushing's syndrome. The demineralization of the bones is attributed to parathyroid gland overactivity because of the frequency with which these glands are enlarged or are the seat of actual adenomatous formation in cases of Cushing's syndrome. In the dog with degeneration of the hypothalamic nuclei and consequent depression of hypophysial basophile cell activity similar to that found in persons with Cushing's syndrome, enlargement of the parathyroids (Fig. 4D) occurs but osteoporosis does not. The failure to develop osteoporosis in the dog in spite of parathyroid enlargement may be related to the lesser degree of degeneration which occurs in the elastic and the connective tissues of the dog's body generally. It is noteworthy that in such dogs the arterial walls do not become infiltrated with calcium as they do in persons with Cushing's syndrome. In man with Cushing's syndrome regardless of the primary cause and in the dog with atrophy of the paraventricular nuclei, the blood calcium and phosphorus levels are not altered appreciably except under rare circumstances.[27]

In renal dwarfism in which the mechanism for the enlargement of the parathyroid glands is similar to that postulated in Cushing's syndrome and in which marked demineralization of the bones occurs frequently, infiltration of calcium salts into the arterial walls occurs as part of the process of the development of arteriosclerosis.

EXPERIMENTAL DATA

Procedure. The median eminence was severed from the overlying hypothalamus (Fig. 6) in ten dogs through the oral approach. Neither the neural nor the glandular hypophysis was removed. Dogs so modified are referred to as "puncture type I." In seven other dogs a transverse lesion was made just rostral to the mammillary bodies to a depth of 8 mm. through the temporal approach. (Fig. 6.) Dogs so modified are referred to as "puncture type II."

Functional studies of the effect of these two operations on the animals were made over varying periods of time ranging from six to ninety months. The studies included observations on appetite, body weight, water intake and output, blood pressure, insulin sensitivity, sugar tolerance, blood sugar, serum calcium, serum phosphorus, plasma proteins, blood non-protein nitrogen, renal clearances and differential blood counts.

Major studies such as renal clearance were carried out on a limited number of dogs. In this report are presented the results obtained on two dogs of the puncture type I class (hereafter referred to as PIA and PIB) and two dogs of the puncture type II class (hereafter referred to as PIIA and PIIB). They are typical of the results found in all other dogs studied with similar hypothalamic lesions.

Results. A rapid and sustained increase in appetite follows both the puncture type I and the puncture type II procedures. Such dogs consume their food ravenously and in large amounts. The increased consumption of food results in a rapid gain in weight.

Puncture type I dogs develop marked sustained polyuria while puncture type II dogs have a normal urine output. This is con-

sistent with other evidence that the loss of the fibers originating in the supraoptic nuclei is of primary significance in the reduction of the antidiuretic hormone of the neural hypophysis.[28] Denervation of the paired supraoptic and paraventricular nuclei

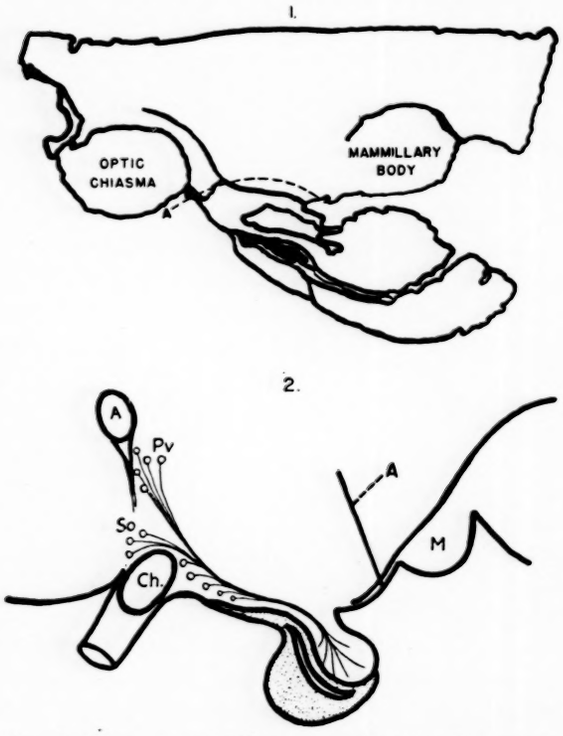

FIG. 6. Diagram to indicate operations to denervate the neural hypophysis in the dog. (1) Complete denervation called puncture type I, performed through the oral approach; (2) partial denervation, puncture type II, by severance of fibers from the thalamus, subthalamus and mammillary bodies to the paraventricular and supraoptic nuclei, performed through the temporal approach.

(puncture type I) or denervation of the paired paraventricular nuclei (puncture type II) results in obesity and changes in sex function.

The blood glucose values (Somogyi method) after sixteen to twenty-four hours of fasting for fifteen normal dogs (based on two to eight observations for each dog) varied from 65 to 80 mg. per cent with an average value of 76 mg. per cent. Values obtained from seven puncture type I dogs ranged from 55 to 87 mg. per cent with an average value of 72 mg. per cent. Values obtained from seven puncture type II dogs varied from 57 to 63 mg. per cent with an average value of 60 mg. per cent.

Glucose tolerance tests on puncture dogs, type I and II, within the first year after operation revealed no alteration from the normal response. Insulin sensitivity tests

TABLE I
INSULIN SENSITIVITY, DOG PIB
Blood sugar response to intravenous administration of insulin, 0.125 units/kg.; blood sugar values in mg. %.

Time after Operation	Time in Minutes Following Administration of Insulin					
	Fasting	30	60	90	180	240
10 Months Weight 15 kg.....	69	57	72	72	72	66
25 Months Weight 40 kg.....	74	52	49	67	74	72

(0.125 units/kg. intravenously) on PIA ten and twenty-five months postoperatively and on PIIA and PIIB twelve months after operation revealed no obvious alteration in sensitivity although no preoperative tests were available for comparison. Similar tests on PIB showed that insulin sensitivity had decreased twenty-five months after the operation. (Table I.) It would be expected that a preponderance of eosinophile cells with overaction would lead to decreased insulin sensitivity.[22]

In this laboratory the average mean blood pressure of normal dogs, measured under nembutal® anesthesia in the third stage of surgical anesthesia, has been found to be 100 mm. Hg. The mean blood pressure is determined by intra-arterial puncture in the femoral artery. The average mean blood pressure for hypophysectomized dogs taken under similar circumstances is 90 mm. Hg. Twenty-two months after operation the mean blood pressure in puncture dog PIA was 105 mm. Hg. This dog's blood pressure measured 140/90 mm. Hg by the cuff method eleven months after operation. Twenty months after operation the blood pressure of PIB measured by the cuff method averaged 170/105 mm. Hg. Later

this dog's mean arterial pressure with or without anesthesia averaged 140 mm. Hg (femoral puncture method). This elevated pressure was maintained until one year before the dog's death seven and one-half years after operation. No observations were made during the last year of its life.

Dog PIIA was sacrificed and autopsied twenty-one months after operation. At this time the mean blood pressure, determined by the femoral puncture method under surgical anesthesia, was found to be 136 mm. Hg. The blood pressure of PIIB taken under similar circumstances twenty-two months after operation was 149 mm. Hg. The highest mean blood pressure recorded in a puncture type II dog was 155 mm. Hg; it was recorded twenty-two months after operation.

TABLE II

RENAL BLOOD FLOW AND MAXIMUM TUBULAR CLEARANCE STUDIES ON PUNCTURE TYPE I DOGS

Date	Blood Pressure (mm. of Hg)	Weight (kg.)	Average Urine Output per Day (cc.)	Diodrast Clearance (cc./min./m²)	Inulin Clearance (cc./min./m²)	D Tm (mg.I/min./m²)	Filtration Fraction
Dog PIA							
1-17-41 7 days postoperative		14.5	5,300	229	80.5	16.7	0.35
1-25-41 15 days postoperative				176.4	70.5	13.1	0.40
3-25-41 74 days postoperative		19.5		273	93.7	19.5	0.34
6-2-41 143 days postoperative		22.5		202	63	19	0.31
12-2-41 326 days postoperative	140/90 cuff method	23.4	5,000	279	93	29.2	0.33
11-9-42 666 days postoperative	105 (mean) femoral puncture method						
Dog PIB							
12-30-40 preoperative		14	800	250	82	13.4	0.35
10-13-41 237 days postoperative		25.7	5,500	251	85	13.3	0.34
1-8-43 689 days postoperative		36.2	5,600	462	129	18.6	0.28
3-26-43 766 days postoperative	136 (mean) femoral puncture method	38	5,500	306	100	28.96	0.23
3-6-44 1111 days postoperative	140 (mean) femoral puncture method	35.9	4,900	338	86	25.67	0.25
11-23-45 1738 days postoperative	140 (mean) femoral puncture method	43.5	4,800	261	110	23.44	0.42

Renal blood flow and maximum tubular clearance studies on puncture type I dogs have been reported previously.[9,29] In Tables II and III are shown the results of our studies in this regard on dogs PIA, PIB, PIIA and

PIIB. They reveal that in the puncture type I dogs two and one-half to eight months after operation the renal blood flow was normal according to the average level for normal dogs obtained in this laboratory. In the puncture type II dogs the renal blood flow was normal when studies were first made at 281 and 348 days after operation.

It is emphasized that hypertension was present in these dogs without any depression of renal blood flow. It was present also when the renal blood flow was greater than normal as in dog PIB. The diodrast Tm studies revealed that with time after operation the maximum tubular excretion increased to above average normal levels. The average Tm values for ten normal dogs was 20 mg. I. per min. per m^2. Values for the two puncture type I dogs, PIA and PIB, reached 29.2 and 28.96 mg. I. per min. per m^2, respectively, at eleven months (dog PIA) and two years (dog PIB) following operation. Values for the two puncture type II dogs, PIIA and PIIB, reached 26.4 and 28.8 mg. I. per min. per m^2, respectively, at ten months (dog PIIA) and one year (dog PIIB) following operation. This augmentation in Tm values is considered an expression of an increased renotrophic influence of the hypophysial eosinophile cells. These values are in contrast with those reached after adrenalectomy in which the hypophysial eosinophile cells are decreased in number. The maximum tubular excretion of diodrast in adrenalectomized dogs maintained on doca pellets averaged 5 mg. iodine per min. per m^2. This is a proportionately greater depression than is the depression of diodrast clearance under such circumstances. In normal and hypophysectomized dogs the administration of adrenal cortical extracts has practically no effect on Tm values whereas anterior pituitary extract elevates them markedly.[9] They are likewise

TABLE III

RENAL BLOOD FLOW AND MAXIMUM TUBULAR CLEARANCE STUDIES ON PUNCTURE TYPE II DOGS

Date	Blood Pressure (mm. of Hg.)	Weight (kg.)	Average Urine Output per Day (cc.)	Diodrast Clearance (cc./min./m^2)	Inulin Clearance cc./min./m^2)	D Tm (mg. I/min./m^2)	Filtration Fraction
Dog PIIA							
1-26-45 281 days postoperative			800	246	93	26.2	0.32
2-9-45 295 days postoperative		19.7	850	270	93	26.4	0.28
5-1-46 741 days postoperative	136 (mean) femoral puncture method	20.9	800				
Dog PIIB							
3-13-45 348 days postoperative		16.5	700	254	109	23.6	0.36
3-20-45 355 days postoperative			750	292	120	28.8	0.34
3-27-45 362 days postoperative				236	115	27.6	0.41
2-6-46 678 days postoperative	149 (mean) femoral puncture method	19.2	800				

markedly elevated by certain growth hormone preparations which, however, may also contain a renotrophic hormone.[30]

Certain other observations pertinent to our problem were made. Denervation of the neural hypophysis (puncture type I) or the interruption of afferent fibers (puncture type II) was without effect on plasma sodium. In puncture type I dogs after renal tubular excretion of diodrast had returned to normal there appeared to be a slight increase in plasma potassium comparable to that found after hypophysectomy, i.e., from an average of 4.85 mEq./L. to 5.35 mEq./L.[18]

TABLE IV

BLOOD STUDIES, DOG PIB

Average of four complete blood counts performed seven years five months following complete neural hypophysial denervation:

R.B.C.	W.B.C.	Baso.	Eos.	Stabs.	Segs.	Lym.	Mono.
6.55	17,300	0.6%	6.5%	0.2%	76.1%	13%	3.5%

Average of thirty-nine complete blood counts performed on seven normal dogs in our laboratory:

R.B.C.	W.B.C.	Baso.	Eos.	Stabs.	Segs.	Lym.	Mono.
7.10	12,500 ±5,000	0%	5.2%	1.1%	62.1%	28.6%	3%

Blood cholesterol values (modified Bloor method) for thirteen normal dogs averaged 140 mg. per cent and for ten puncture type I dogs averaged 194 mg. per cent. Twenty-two months after the operation the blood cholesterol for PIIA was 234 mg. per cent and that for PIIB was 201 mg. per cent. The serum calcium values for dogs of both puncture types were normal.

The long-term effect of the puncture type I operation on the circulating blood cells is shown in Table IV. The lymphopenia and neutrophilia are similar to those found in persons with Cushing's syndrome. No observations were made on the circulating blood cells of puncture type II dogs.

Anatomic Data

At the end of the period of observation each animal was autopsied completely. The brain was perfused with 10 per cent formalin. The other tissues were fixed in formol-Zenker's solution. The hypothalamus was sectioned serially at 20 microns. Every third section was stained with cresyl violet. The hypophysis was sectioned serially at 5 microns and stained according to the method of Rasmussen. Typical glandular hypophysial sections were differentially counted according to the method described by Rasmussen and Herrick.[31] All other tissues including the endocrine glands were studied.

PIA. The dog showed marked obesity. This dog was full-grown at the time of operation and weighed 12.2 kg.; at autopsy twenty-two months later it weighed 25 kg. The increase in fat was especially apparent in the subcutaneous tissues, omentum and retroperitoneal tissues. The thymus gland was atrophic. The heart showed concentric hypertrophy of the left ventricle of moderate degree, the thickness of the left ventricle being 1.2 cm.; the heart weighed 130 gm. (normal 85 to 90 gm.). The adrenal glands together weighed 1.9 gm.; the cortex of each gland was definitely thickened. The kidneys were normal in appearance; the right weighed 37 gm. and the left 38.5 gm. The combined weight of the thyroid glands together with the enlarged parathyroid glands was 1.26 gm. The parathyroids were enlarged to twice their normal size. The ovaries were large and of the mulberry type due to the presence of many large corpora lutea. The liver, pancreas and intestines showed no gross abnormalities. The uterus and fallopian tubes were atrophic.

PIB. The dog showed marked obesity with the fat distribution similar to that of PIA. This dog was full-grown at the time of operation and weighed 15 kg.; seven and one-half years later it weighed 47 kg. The thymus gland appeared atrophic and weighed only 2.8 gm. The heart weighed 175 gm. and showed marked concentric hypertrophy of the left ventricle; the thickness of the left ventricular wall was 1.7 cm. (Fig. 4A.) The aorta was increased to twice the average normal thickness in its thoracic and abdominal portions. There were a few pin-head sized, elevated, yellowish plaques on the intima in the upper thoracic portion. (Fig. 4B.) The elastic tissue fibers of the aorta showed considerable fragmentation. Micro-incineration studies of the sections revealed scattered areas of infiltration of the wall by calcium salts but not to a degree comparable with that seen in sections of human aortas involved in an arteriosclerotic process. The pancreas was normal in appearance; it

weighed 32.2 gm. The kidneys were normal in appearance except for an estimated 70 per cent enlargement. Each weighed 74.0 gm. The adrenals were hypertrophied (Fig. 4C); their combined weight was 3.8 gm. The spleen was small; it weighed 25.0 gm. The combined weight of the thyroid glands together with the enlarged parathyroid glands was 1.6 gm. The parathyroid glands were enlarged to six times the normal size. (Fig. 4D.) The uterus and fallopian tubes were atrophic.

PIIA. The dog showed definite obesity with fat distribution similar to that of PIA. This dog was full-grown before operation and weighed 13.2 kg. At the time of autopsy two years after puncture operation its weight was 20.9 kg. The thymus gland was atrophic. The heart weighed 133 gm. and showed moderate concentric hypertrophy of the left ventricle. The aorta showed no obvious changes. The adrenals were somewhat enlarged, their combined weight being 1.92 gm. The liver, pancreas and other viscera appeared normal. The combined weight of the thyroid glands together with the parathyroid glands was 0.94 gm. Each kidney weighed 34.0 gm. The ovaries were enlarged due to large corpora lutea. The uterus and fallopian tubes were atrophic.

PIIB. The dog showed definite obesity. This dog was full-grown before operation and weighed 9 kg. At the time of autopsy twenty-three months after puncture operation its weight was 19.2 kg. The thymus gland was atrophic. The heart weighed 99 gm. and showed moderate concentric hypertrophy of the left ventricle. The aorta showed no obvious abnormality. Each kidney weighed 31.0 gm. The combined weight of the adrenals was 1.66 gm. The ovaries were enlarged; they were mulberry-like in shape due to enlarged corpora lutea. The fallopian tubes and uterus were atrophic. The combined weight of the thyroid glands together with the parathyroid glands was 0.97 gm. The liver, pancreas and viscera appeared normal.

Microscopic Findings

PIA. Stained serial sections of the hypothalamus showed that retrograde degeneration of the cells of the supraoptic nucleus was complete. Fifty per cent of the cells of the rostral and ventral portions of the paired paraventricular nuclei failed to stain. These findings are similar to those for all well punctured dogs of the type I class.[32] The neural hypophysis showed marked atrophy with disappearance of the pituicytes. The glandular hypophysis showed a complete absence of all basophile cells with an increase in eosinophile cells which were well granulated. The chromophobes revealed no abnormalities. A differential count revealed 35.8 per cent chromophobes, 64.2 per cent eosinophiles and 0.0 per cent basophiles. The normal differential count of the dog's glandular hypophysis obtained in this laboratory, chromophobes 52.3 per cent, eosinophiles 38.5 per cent and basophiles 9.2 per cent, is comparable to that in man.[33,34] The thyroid glands showed changes similar to those observed after hypophysectomy. The acinar cells were flattened and there was a marked diminution in the amount of colloid formation. The parathyroid glands showed normal-appearing cells of the principal type. The pancreas showed acinar tissue of normal type. The islet cells were in small, loosely packed clusters; both alpha and beta cells were present and of normal appearance. If any change was present in the islets, it consisted essentially of a reduction in cell number. The adrenals showed marked hypertrophy of the fascicular layer and moderate hypertrophy of the reticular layer; the zona glomerulosa was well developed. The ovaries exhibited regressive changes in the follicles which showed no evidence of maturation. The corpora lutea were large and highly vascular; their cells appeared active. There were no corpora lutea atretica. The kidneys showed no abnormalities of the tubular cells or of the glomeruli. The blood vessels appeared normal.

PIB. The hypothalamus showed changes similar to those described for PIA. The neural hypophysis was atrophic. The glandular hypophysis showed a striking change from that observed in PIA. The eosinophiles present were normal in appearance; the granules were prominent and stained well. The chromophobes appeared normal. The basophile cells were greatly increased in number and they showed marked degranulation with and without hyalinization (Fig. 4E), such as is observed in Cushing's syndrome. A differential count revealed 36.4 per cent chromophobes, 24 per cent eosinophiles and 39.6 per cent basophiles. The adrenal glands showed marked hypertrophy of the zona fasciculata and a lesser degree of hypertrophy of the reticular zone. (Fig. 4G.) The zona glomerulosa and the medulla appeared normal. The kidneys showed no degenerative changes.

Their enlargement was the result of an increase in size of the tubular cells and of the glomeruli. (Fig. 5D.) The acinar tissue of the pancreas showed no change from the normal. There was a marked decrease in size of the islets with the cells so loosely spaced that with low magnification the islets were difficult to recognize. (Fig. 5B.) This condition is in striking contrast to that found three years after the original puncture operation in biopsy tissue from the head, the body and the tail of the pancreas. At that time the islets were normal in size and compactness. (Fig. 5A.) Differential stains revealed both alpha and beta cells to be present in the islets at the time of autopsy. The thyroid gland showed marked atrophic changes. (Fig. 4F.) At the periphery there were a few large follicles containing hard colloid. Generally the acini were conglomerated and exhibited marked desquamation of the acinar cells. The amount of colloid was greatly reduced and that which remained showed partial vacuolization. No signs of acinar cell regeneration were present. There was marked arterial degeneration throughout the gland. The small arterioles showed hyaline degeneration of the media. The intimal cells showed proliferation causing occlusion of the lumen. The parathyroid glands consisted of closely packed principal cells of normal appearance. (Fig. 4H.) The ovaries were small and markedly atrophic. Scarcely any recognizable follicles remained and those remaining had become cyst-like. (Fig. 4I.) There were numerous cysts present which were lined with flat epithelial cells. No corpora lutea were recognizable. There was marked scarring present. The arteries were thick-walled and had small lumens. The uterus and fallopian tubes were markedly atrophic.

PIIA. The supraoptic and the paraventricular nuclei were normal in appearance. Scarring was present rostral to the mammillary bodies due to the lesion made at the time of operation. The neural hypophysis was normal in size and appearance. The glandular hypophysis was normal in size. There was a marked change in its cell composition. The eosinophiles were increased in number and closely packed as in PIA; the granules were prominent and highly eosinophilic. The basophiles were reduced in number and those which remained showed a decrease in the number of granules with faint staining. The chromophobes were normal in appearance. The thyroid gland showed no obvious change from the normal microscopic appearance. The adrenal glands showed a 15 per cent to 20 per cent thickening of the cortex when compared with the average normal gland of dogs of similar size. This thickening involved particularly the zona fasciculata and to a lesser degree the zona reticularis. The kidneys, liver and pancreas showed no recognizable change from the normal. The ovaries showed regressive changes in the germinating layer with the retention of large vascular corpora lutea. The uterus and fallopian tubes were atrophied.

PIIB. The microscopic appearances of the hypothalamus, the hypophysis and the other organs were similar to those found in PIIA. A differential cell count of the glandular hypophysis showed chromophobes 46.0 per cent, eosinophiles 52.5 per cent and basophiles 1.5 per cent.

ANALYSIS OF FUNCTIONAL AND ANATOMIC EXPERIMENTAL DATA

Analysis of the functional and anatomic changes in the dog, which follow complete denervation of the neural hypophysis or its depression by interruption of nervous pathways coming to it from the thalamus, the subthalamus and the mammillary bodies, indicates that preponderance and overaction of the hypophysial eosinophile cells result together with reduction and underaction of the hypophysial basophile cells. A consequence of the eosinophile overaction is stimulation of the adrenal cortex, the corpora lutea, the androgenic cells and the renal tubule cells. Eosinophile overaction also results in a depression of the cells of the islets of Langerhans and of the thymus. Depression of basophile cell function causes depression of and regressive changes in the thyroid gland and depression of maturation of the ovarian follicles and of the seminiferous tubule cells. It permits hypertrophy with overaction of the parathyroid glands.

In the dog this production of glandular imbalance is responsible for the development of increased appetite, obesity, decreased insulin response, hypertension of the diastolic type, and cardiac, adrenal, renal and parathyroid hypertrophy. Hypercholesteremia and potassium retention are

found also. In man, as shown in Cushing's syndrome, diabetes mellitus, arteriosclerosis and demineralization of bone also occur.

COMMENT

An analysis of the clinical and pathologic data on persons exhibiting Cushing's syndrome due to a lesion primary in the hypothalamus reveals consistent evidence of enlargement and overaction of the adrenal cortex, particularly of its inner two layers which are under the trophic influence of the glandular hypophysis.[11] In the female enlargement of the corpora lutea and overaction of the androgenic cells are also found. In the male the interstitial cells of the testis are well preserved or increased in number. It has been shown experimentally in the dog that these manifestations reflect overaction of the hypophysial eosinophile cells. In the dog an atrophy of the thyroid gland and an elevation of the plasma cholesterol also occur. In the female dog there is depression of maturation of the ovarian follicles and in the male failure of maturation of the seminiferous tubule cells. These physiologic changes in the dog have been correlated with suppression of maturation of the hypophysial basophile cells.

Cushing's syndrome, regardless of its primary origin, represents a resultant endocrine imbalance in favor of the hypophysial eosinophile cells and of those structures to which they are trophic. The hypophysial basophile cells and the structures to which they are trophic show functional depression and regressive changes.

The degranulated hypophysial basophile cells, with or without hyalinization, which characterize all cases of Cushing's syndrome are considered to reappear (after their initial disappearance) following the depression of the thyroid gland, the ovarian follicles and the seminiferous tubule cells which occurs in these cases. This interpretation is based on the similarity of these changes in the basophiles to those which follow thyroidectomy or gonadectomy or both together in animals.[35] The altered basophiles which result from gonadectomy may be functionally active because of the observation that castration of one parabiotic rat effects enlargement of the gonads of its partner. In addition by castration, continuous estrus has been produced in the non-castrate partner.[36] In the puncture dogs, which are considered to be the experimental counterpart of those cases of Cushing's syndrome due to an atrophy of the paraventricular hypothalamic nuclei, the evidence does not indicate that the hyalinized basophile cells are functionally effective. It is suggested that the marked suppression of the hormone of the neural hypophysis interferes either with the basophile cells' capacity to secrete an effective hormone or else to discharge it. It might be argued that the hormone is ineffective because of the marked atrophy of those target organs to which the hypophysial basophiles are trophic. This is regarded as improbable for the following reason: In man exhibiting hyalinized hypophysial basophiles the histologic changes of a regressive character present in the end organs do not appear sufficient to exclude the probability of stimulation by an effective basophile cell hormone.

The basophile cells become degranulated also in those instances in which a tumor of the adrenal cortex is the primary lesion of Cushing's syndrome. In two such instances in our experience the supraoptic and the paired paraventricular hypothalamic nuclei have been found to be normal histologically. There has been no compression of the ependymal lining cells of the third ventricle to indicate an increase in intraventricular pressure. To explain the basophile cell hormone ineffectiveness in such cases it is suggested that normally a balanced antagonistic relationship exists between certain hormone factors of the neural hypophysis and of the adrenal cortex. As revealed in dogs of both puncture types, depression of the neural hypophysial hormone factors, particularly those essential for the maturation of the basophile cells, leads to overaction of the metabolic- and sex-controlling hormones of the adrenal cortex. In the puncture type II dog the operation does

not cause diabetes insipidus. This presumably is because the supraoptic nucleus, which controls the secretion of the neural hypophysial antidiuretic hormone, is not depressed sufficiently by the puncture type II operation. However, as a result of both puncture type operations the trophic influence of the paraventricular nucleus is sufficiently depressed to effect a depression of those neural hypophysial hormone factors responsible for hypophysial basophile cell maturation.

Degranulation of the hypophysial basophile cells occurs also when the primary lesion responsible for Cushing's syndrome is an ovarian tumor.[37] For such a tumor to produce overaction of the eosinophile-adrenal hormone complex it would have to secrete progesterone.[10] It has been established that progesterone neutralizes, *in vitro*, the effect of posterior pituitary hormone on the estrogen-primed uterine muscle.[38] Presumably it also counteracts those hormone factors of the neural hypophysis which are in balanced antagonistic relationship with the adrenal cortex. This would explain the hypertrophy of the adrenal cortex which occurs in Cushing's syndrome due to an ovarian tumor.[37] Purely androgenic tumors of the ovary do not modify the glandular hypophysis sufficiently to lead to the endocrine imbalance which results in Cushing's syndrome.

It is known that tumors of the pancreas[39] and probably also those of the thymus and the parathyroid gland are found in persons with Cushing's syndrome in a somewhat higher incidence than in the general population. From the evidence that Cushing's syndrome always is associated with overaction of the hypophysial eosinophile-adrenal cortical hormone complex and that this complex is without influence on the acinar tissue of the pancreas but is inhibitory to its islet cells, it follows that actively secreting primary tumors of the pancreas would not be expected to produce Cushing's syndrome. Likewise an actively secreting thymic tumor would inhibit the hypophysial eosinophile-adrenal hormone complex rather than stimulate it (unpublished data in this laboratory). If the development of tumors of the pancreas and of the thymus is related to the glandular imbalance of Cushing's syndrome, it would seem to be only as a consequence of prolonged depression of these structures. An actively secreting parathyroid tumor would inhibit the hypophysial basophile cells[3] but would not alter the activity of the eosinophile cells. The depression of the basophile cells as seen in Cushing's syndrome could lead, however, to hypertrophy of or adenoma formation in the parathyroid glands.

SUMMARY

Cushing's syndrome may have three primary causes, a tumor of the adrenal cortex, atrophy of the paired paraventricular hypothalamic nuclei or a tumor of the ovary secreting progesterone.

These primary causes effect an endocrine imbalance characterized by overaction of the hypophysial eosinophile cells and underaction of the hypophysial basophile cells. Later, because of atrophic changes in the thyroid gland and the gonads, the basophile cells may increase above normal numbers. In spite of this increase in numbers these cells are hyalinized and functionally depressed, possibly because of the associated depression of the secretion of the neural hypophysis.

The imbalanced relationship between the hypophysial eosinophile and basophile cells results in an augmentation of function of those structures to which the eosinophiles normally are trophic, namely, the adrenal cortex, the corpora lutea, the androgenic cells and the renal tubule cells. Depression of hypophysial basophile cell function results in a depression of the thyroid gland and a failure of maturation of the ova and of the seminiferous tubule cells. Overaction of the eosinophile cells depresses the islet cells of the pancreas and the thymus gland. Underaction of the hypophysial basophile cells allows overaction of the parathyroid glands.

These endocrine imbalances result in the signs and symptoms which characterize

Cushing's syndrome such as polyuria, polydipsia, polyphagia, obesity, diabetes mellitus, diastolic hypertension, arteriosclerosis, osteoporosis and a depression of maturation of the ova or of the spermatogenic cells.

It is stressed that a dual origin, primary either in the central nervous system or in a peripheral endocrine gland, pertains not only to Cushing's syndrome but also to many other endocrine disorders.

Experimentally in the dog many of the bodily changes which characterize Cushing's syndrome in man result from either denervation of the entire neural hypophysis with retrograde degeneration of the supraoptic and paraventricular hypothalamic nuclei or interruption of afferent pathways caudal to the paired paraventricular nuclei.

Tumors of the thymus or of the pancreas occasionally found in association with Cushing's syndrome are not considered to be primary causes of the syndrome but are believed to arise in these structures coincidentally. It is of interest to note that in Cushing's syndrome these structures are depressed by the eosinophile cells of the glandular hypophysis which normally are inhibitory to them. Tumors of the parathyroid gland are believed to arise because of the lessening of inhibitory influences from the hypophysial basophile cells.

Based on the experimental and clinical observations herein reported, a concept is offered to explain the pathogenesis of the various pathologic states such as obesity, polyuria, diabetes mellitus, diastolic hypertension and osteoporosis which develop in persons with Cushing's syndrome.

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Effects of Adrenocorticotropic Hormone (ACTH) in Gout*

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THE indications for the use of ACTH in the treatment of gout are uncertain at present and somewhat confused. Recent reports[1–8] indicate that ACTH effects amelioration of the local and systemic manifestations of acute gouty arthritis, sometimes dramatically and in patients responding unsatisfactorily to colchicine. On the other hand, an exacerbation, generally interpreted as the precipitation of a new attack, has been found to occur within two or three days after discontinuance of therapy, suggesting the conjoint use of colchicine. Moreover administration of ACTH has been observed to provoke acute gouty attacks in interval gout. It would appear, therefore, that ACTH is capable both of terminating and eliciting acute gouty arthritis. This apparently dual and contrary action has made the place of ACTH in the therapy of gout uncertain and has inspired much speculation, particularly concerning the role of the pituitary and adrenal glands in the pathogenesis of gout.

More data on these points are desirable and we are therefore reporting our observations in acute and interval gout.

MATERIAL AND METHODS

Observations in acute gouty arthritis were made in eleven attacks occurring in ten patients, Case V. P. being studied in two successive attacks. ACTH was usually given for four days in dosages of 100, 55, 30 and 20 mg. per day, in four divided doses each day. The action of ACTH in interval gout was investigated eight times in five patients, most patients receiving 100 mg. per day for four days, in four divided doses each day. All patients were hospitalized and placed on a low-protein, low-purine diet before and during ACTH therapy.

Uric acid determinations in serum and urine were made by a modification of the method of Buchanan, Block and Christman[9] incorporating the use of uricase, urea cyanide-carbonate and arsenophosphotungstic acid. In a few instances when salicylates were employed, chromogenic interference by gentisic acid was obviated by prior extraction with ethyl ether.[10] In no instance was enough glucose found in the urine to give significant chromogen.[11] Eosinophile counts were made by the phloxine method.[12]

RESULTS

Effects of ACTH in Acute Gouty Arthritis (Table 1). Of the eleven cases of acute gouty arthritis treated, seven showed a satisfactory response to ACTH. Patient J. M., who was treated on the fourth day after onset of an acute attack involving the left great toe and ankle, had complete relief of symptoms and signs with return of temperature to normal within twelve hours of therapy comprising 50 mg. ACTH. He remained symptom-free during continuation and after discontinuance of ACTH. Patient H. C., whose acute multiple joint involvement failed to respond to apparently full doses of colchicine given elsewhere for two weeks, showed marked amelioration of pain, swelling and redness of joints and fever twelve hours after receiving 50 mg. ACTH. The improvement could then be maintained with colchicine. Patient D. W. for several months had had almost un-

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TABLE I—EFFECTS OF ACTH IN ACUTE GOUTY ARTHRITIS

Case	Age	Duration of Gout (yr.)	Tophi	Acute Gouty Arthritis			ACTH dosage (mg./day)	Response to ACTH			
				Location	Severity	Duration (days)		Eosinophiles mm³	Uric Acid: Urine (mg./24 hr.)	Uric Acid: Serum (mg.%)	Clinical
J. M.	42	2½	None	Great toe and ankle	+++	4	100,55,30,20	116 → 25	290 → 574	8.5 → 5.8	Rapid relief; no recurrence
H. C.	61	4	None	Knee, foot, wrist, elbows	++++	14	50,——	.....	.....	.....	Dramatic response, maintained by colchicine therapy without relapse
D. W.	52	15	None	Knees, ankles, feet	++++	Several months	100,55,30,20	106 → 6	751 → 927	7.6 → 7.5	Almost complete relief after 24 hr.; mild recurrence 6 days after last dose, controlled with aspirin
P. M.	70	34	None	Knee	+++	7	100,55,30,20	110 → 13	640 → 834	6.1 → 5.3	Complete relief after 24 hr.; mild recurrent attack 2 days later, subsided spontaneously
M. K.	69	36	Extensive	Hand	++	3	100,55,30,20	500 → 31	800 → 1124	11.9 → 7.9	Complete relief within 48 hr.; mild recurrence 45 hr. after last dose; full-blown attack 5 days later, controlled by colchicine
D. R.	34	6	Ear	Foot	++++	10	100,70,45,55	369 → 16	904 → 1086	11.5 → 11.1	Practically symptom-free 36 hr. after beginning ACTH therapy; mild pain when dose was cut on 3rd day; symptom-free on 4th day; recurred 8 hr. after cessation of ACTH, controlled by colchicine
L. T.	46	15	Ear, hands, arms, feet	Elbow, toes	++	1	80,80,80,60	390 → 6	750 → 935	9.2 → 5.7	Symptom-free after 24 hr.; mild pain on 4th day when ACTH reduced, relieved by increasing dose. Marked fluid retention on ACTH. Recurrence of gout when ACTH stopped, controlled with colchicine
V. P.	59	20	Extensive	Hands, elbows, shoulders, sternoclavicular joint	++++	1	100,55,30,20	100 → 0	419 → 816	12.3 → 10.4	Partial relief only; attack was terminated by colchicine
V. P.	..	....	.....	Hand	++++	3	100,55,30,20	19 → 38	894 → 871	7.5 → 6.8	Partial relief only; attack was terminated by colchicine
J. P.	56	30	None	Great toes, foot, knee	+++	2	75,65,——	.....	.....	.....	Somewhat improved after 3 doses of ACTH, when dosage was reduced; controlled by colchicine
E. S.	42	14	Ear	Foot, knee	+++	1	100,100,100,100	356 → 75	862 → 1645	11.7 → 9.9	Worse during first 2 days of treatment; somewhat improved on 3rd day but attack then spread to other joints; finally terminated by colchicine and aspirin

interrupted acute gouty attacks migrating from feet to ankles to knees. There was complete subsidence of pain and fever in twenty-four hours during which time he received 100 mg. ACTH, and marked relief of joint swellings over the next three days of treatment. Patient P. M. experienced complete relief of acute gouty arthritis involving the left knee within twenty-four hours, during which time he received 100 mg. ACTH. In patient M. K. there was complete subsidence of pain, redness and swelling of the left hand, with return of the temperature from 103°F. to normal, within forty-eight hours of onset of therapy comprising 150 mg. ACTH. Patient D. R. also showed marked amelioration of signs and symptoms involving the right foot within thirty-six hours of onset of therapy but recurrence of pain as the dosage of ACTH was reduced on the third day necessitated an increase to 45 and 55 mg. on the third and fourth days, respectively, with complete control of symptoms until discontinuance of therapy. Patient L. T., who had arteriosclerotic heart disease with electrocardiographic evidence of extensive myocardial damage and one episode of frank cardiac failure three months before, as well as intermittent gout for fifteen years, developed acute gouty olecranon bursitis on the right side and involvement of the toes of both feet. The day after onset he received 80 mg. ACTH in four divided doses over twenty-four hours and was completely freed of pain. Swelling and joint stiffness disappeared in the course of the next day. However, oliguria developed, with retention of sodium and 2 kg. of water in the first two days of treatment.* In view of threatened cardiac failure, he was given 2 cc. mercuhydrin on the third day of ACTH therapy. He diuresed satisfactorily and remained free of complaints. As the dosage of ACTH was reduced on the fourth day to 10 mg. every six hours, he had mild recurrence of joint pains which disappeared when the last two doses were increased to 20 mg. each. There was recurrence of stiffness, later also of pain, on discontinuance of ACTH therapy. These symptoms were controlled with colchicine which he had been taking regularly for years.

Three patients responded unsatisfactorily to ACTH. In one severe attack involving the hands, elbows, shoulders and sternoclavicular joints, V. P. experienced only partial relief of joint pain, swelling and redness after four days of therapy totalling 200 mg. ACTH; the temperature, however, fell from 102°F. to normal. It was necessary to resort to colchicine which effected complete relief. A second attack involving the left hand two months later responded somewhat better to ACTH but again was inadequately controlled until colchicine was employed. In patients J. P. and E. S. the effects of ACTH on both joint symptoms and systemic manifestations were unimpressive and transitory. The attacks were finally controlled with colchicine.

It will be noted in Table 1 that even in those patients who failed to show a satisfactory clinical response to ACTH the characteristic eosinopenia,* increase in urinary uric acid excretion and decrease in serum uric acid level were elicited. Worthy of note, however, is the fact that none of our patients, even those that did well with ACTH, showed a fall in the elevated erythrocyte sedimentation rate under treatment.

In three of these patients with acute gouty arthritis the use of ACTH had definite advantages over colchicine. In Case H. C. a severe attack which had resisted two weeks of apparently full colchicine therapy responded promptly to ACTH. In cases D. W. and J. P. the complication of bleeding from the gastrointestinal tract made the prospect of vomiting and diarrhea with colchicine hazardous whereas ACTH could be given without incurring this risk. In the

* Sodium and water retention of marked degree occurred on both occasions when this patient was treated with ACTH. L. T. was the only patient in our series who suffered any significant side reaction during the short course of ACTH therapy given.

* We have observed a general downward trend in eosinophile counts during the acute stages of gout, which certainly imposes considerable stress, even prior to ACTH therapy. This was most evident in case V. P. (Table 1.)

remaining cases, although the response to ACTH was gratifying and very rapid in some, it did not always seem better than our previous or subsequent experience with these patients when treated with colchicine alone. Four attacks of acute gout partially or wholly resistant to ACTH yielded to colchicine.

Of seven patients whose clinical response to ACTH was complete or virtually complete, discontinuance of ACTH was not followed by exacerbation of symptoms in one (J. M.) who received no colchicine subsequently and in another (H. C., subject to frequent attacks in the preceding two years) who did take colchicine thereafter. D. R. and L. T. had recurrence of symptoms eight hours after cessation of ACTH therapy, responding to colchicine. Patient P. M. experienced mild joint pains two days after discontinuance of ACTH, these subsiding spontaneously. Patient D. W. had mild recurrence of joint pains six days after termination of ACTH therapy; these were readily controlled with salicylates. In the seventh case (M. K.) there was mild recurrence of joint symptoms two days after discontinuance of ACTH. Five days later he developed a full-blown acute attack involving the hands and shoulders with diffuse aches and pains; this responded well to colchicine. In general, however, such exacerbations as we have noted following termination of ACTH therapy suggested re-exhibition of the underlying disease when the suppressive effect of ACTH was discontinued, in the manner that this occurs in rheumatoid arthritis, for example, rather than the initiation of a new attack of acute gout.

TABLE II—EFFECTS OF ACTH IN INTERVAL GOUT

Case	Age	Duration of Disease (yr.)	Tophi	ACTH dosage (mg./day)	Other Medication	Response to ACTH			Acute Attack after Cessation of ACTH
						Eosinophiles mm³	Uric Acid		
							Urine (mg./24 hr.)	Serum (mg.%)	
M. K.	69	36	Extensive	100,100,100,100	None	520 → 0	727 → 1014	11.7 → 8.6	Yes
V. P.	59	20	Extensive	100,100,100,100	None	31 → 0	311 → 666	9.8 → 8.0	No
J. J.	77	8	Extensive	100,55,30,20	None	140 → 0	150 → 308	9.8 → 7.3	No
O. G.	46	2	None	100,100,100,100	None	63 → 0	346 → 698	10.0 → 5.5	No
O. G.	..	..	.....	100,55,30,20	None	62 → 13	357 → 515	8.7 → 7.0	No
O. G.	..	..	.....	100,100,100,100	Carinamide 12 gm. daily before and during ACTH	106 → 6	653 → 670	5.7 → 4.0	No
V. P.	59	20	Extensive	100,100,100,100	Aspirin and $NaHCO_3$ $\overline{aa}$ 5.2 gm. daily before and during ACTH	94 → 0	694 → 922	7.8 → 5.8	No
L. T.	46	15	Ear, hands, arms, feet	100,100,25,*—	Aspirin and $NaHCO_3$ $\overline{aa}$ 5.2 gm. daily before and during ACTH	490 → 0	824 → 841	5.9 → 5.0	No

* ACTH was stopped because of marked fluid retention in this patient with arteriosclerotic heart disease.

Effects of ACTH in Interval Gout (Table II). No apparent clinical change was noted during ACTH therapy, usually 100 mg. per day for four days, in symptom-free intervals of gout. However, every patient showed a marked eosinopenia and, when

not receiving prior treatment with uricosuric agents, a marked increase in urinary uric acid excretion with associated fall in serum uric acid levels.

Following cessation of therapy acute gouty arthritis developed only once (Case

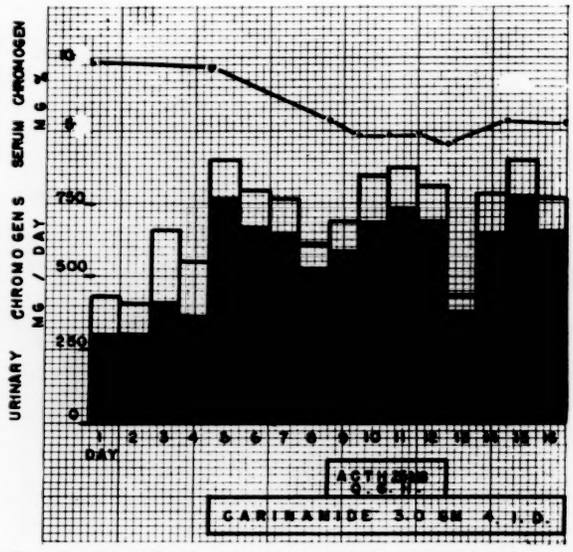


FIG. 1. Case O. G., showing uricosuric action of carinamide and absence of increased uricosuria when ACTH was administered in addition to carinamide. Black area uric acid; open column, non-urate chromogen.

M. K.) in eight trials, in this instance as moderately severe pain, redness and swelling of the left hand and foot, with fever, appearing forty-eight hours after the last dose of ACTH.

ACTH as Uricosuric Agent in Chronic Tophaceous Gout. The action of ACTH in increasing the excretion of uric acid in the urine is a function of dosage, of course, usually becoming insignificant, in our experience, when doses are reduced to 20 or 30 mg. ACTH daily or less. As indicated in Tables I and II, however, even when the same dosage of ACTH is employed there is wide variation from patient to patient in the degree and duration of uricosuria. This would seem to depend largely on whether or not the capacity of the kidney to excrete uric acid is impaired, on the extent of the miscible pool and deposits of uric acid that can readily be mobilized, the rate of uric acid turnover and other factors.

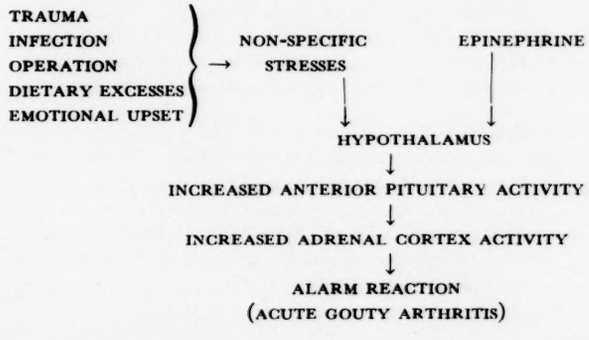
There has been some discussion as to whether the increased urinary uric acid excretion observed with ACTH is due to increased catabolism of nucleoprotein and other uric acid precursors or chiefly to effects on the kidney promoting renal clearance of uric acid. Since the serum levels of uric acid usually fall in association with increased urinary uric acid excretion, often markedly so (Tables I and II), it is apparent that no very great increase in uric acid production occurs. We have also found that the degree of increase in urinary uric acid excretion, while it may exceed 100 per cent, is within the range of that observed with such uricosuric agents as salicylate and carinamide,[13] which suppress tubular reabsorption of urate. Moreover, Stetten,[14] using intravenously injected N^{15} labeled uric acid as a measure of turnover rate, found no indication after ACTH administration of accelerated isotope dilution, hence no evidence of increased uric acid formation. A further indication that the principal mechanism by which ACTH increases urinary acid excretion is chiefly through depression of tubular urate reabsorption, is given by data included in Table II, which do not, however, exclude the possibility of some increase in uric acid formation. Patients O. G., L. T. and V. P. were administered sufficiently large doses of aspirin and sodium bicarbonate, or of carinamide, to cause marked suppression of tubular urate reabsorption with consequent markedly increased urinary uric acid excretion. When the action of ACTH was then superimposed, no significant further increase in urinary uric acid excretion was observed in patients O. G. (Fig. 1) and L. T.; in the case of V. P. the increase was 33 per cent as compared with 114 per cent when ACTH was given without prior treatment. Just how ACTH affects the tubular reabsorptive mechanism for urate, a mechanism which has been shown to be "active" and of limited capacity,[15,16] presumably enzymatic, has yet to be elucidated.

In our experience, the use of ACTH as a uricosuric agent to prevent or treat chronic tophaceous gout is, for the present, neither

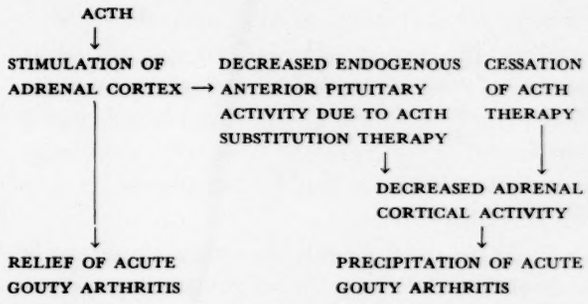
feasible nor desirable. Relatively large doses are required and, as the uricosuric effect of ACTH is transitory, ceasing shortly after discontinuance of therapy (and is often followed by a period of urate retention), continued treatment would be required. Moreover, as shown elsewhere,[13] the increase in urinary uric acid excretion effected by ACTH, even in doses of 100 mg. daily, is of lesser magnitude than can be obtained in many cases by the use of adequate doses of salicylate plus sodium bicarbonate, or of carinamide, uricosuric agents which are readily available and orally administered.

COMMENTS

The effects of ACTH and cortisone in gout have been quite literally interpreted by some to indicate that the pituitary and adrenal glands play a central role in the pathogenesis of gout. According to one view, most clearly expressed by Hellman,[3] the various precipitating causes of gout such as trauma, infection, operation, dietary excesses, emotional upsets, etc., may be classified as non-specific stresses (in the sense of Selye's views) which elicit an alarm reaction taking the form, in the individual predisposed to gout, of acute gouty arthritis.



Since this would not explain the therapeutic effect of ACTH in acute gout, a more general scheme has been proposed by others to account for the dual termination and precipitation of acute gouty arthritis ascribed to ACTH in the literature but confirmed only in part by our own experience.



Wolfson[7,17] has further postulated an additional abnormal adrenocortical androgen and an imbalance in secretion of various 11-oxysteroids.

Ingenious and stimulating as these theories are, they appear not to take into sufficient account a number of pertinent considerations, such as: (1) The diversity of disorders favorably affected by ACTH and cortisone, implying that the action of these agents is not upon primary causal mechanisms but through some peripheral tissue response common to a wide variety of diseases. (2) Disorders of the anterior pituitary gland or of the adrenal glands associated either with hypo- or hyperfunctional states are not associated with gout. (3) There is no convincing evidence that the therapeutic action of colchicine in gout is through the so-called pituitary-adrenal axis.

SUMMARY

1. ACTH effected a very rapid and satisfactory response in the local and systemic manifestations of acute gout in seven of eleven cases treated, including one patient refractory to colchicine. ACTH therefore appears to be a useful agent in the therapy of acute gout. In many of these patients, however, ACTH was not convincingly superior to colchicine, and in four instances colchicine terminated attacks responding unsatisfactorily to ACTH. Unlike colchicine, ACTH is not suitable for prophylactic use in the prevention of acute gouty attacks.

2. Exacerbation of symptoms occurred in four patients following discontinuance of ACTH therapy after a satisfactory response. Such exacerbations usually sug-

gested re-exhibition of the underlying disease upon termination of the suppressive effects of ACTH rather than initiation of a new attack of acute gout. The conjoint and continued prophylactic use of colchicine seems rational in patients subject to frequent recurrences.

3. Acute gouty arthritis developed only once in eight cases of interval gout when ACTH was given in full dosage and then abruptly discontinued.

4. In the prevention and treatment of chronic tophaceous gout, the use of ACTH* is neither feasible nor desirable at present. Salicylates and carinamide are at least as effective uricosuric agents, are readily available and orally administered.

5. The available evidence does not appear to justify the view that the pituitary and/or adrenal glands play a central role in the pathogenesis of gout.

* We are indebted to Dr. John R. Mote, Armour Laboratories, for the supply of ACTH.

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Increased Renal Excretion of Urate in Young Patients with Gout*

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ALTHOUGH urate is known to be present in excess in the gouty patient, it is still not known whether this abnormal accumulation is effected by an overproduction of the substance or a diminution in its destruction or excretion. In view of the fact that urate appears to be excreted chiefly by the kidney[1,2,3] it might seem easy to determine whether an excess is being formed or whether too little is being excreted. However, the advanced age of the usual gouty subject when studied and the damaging effect of urate itself on the kidney[3] made it extremely difficult for earlier investigators to determine whether the reduced renal excretion of urate usually found in the gouty individual initiated and was responsible for the excess urate in the body or whether the reduced renal excretion was caused by the excess urate and the arteriosclerosis frequently present in the older individuals studied. Moreover, the unreliability of earlier methods for the determination of urate prior to 1930, the absence of precise methods for determination of the general integrity of renal function and the earlier lack of information concerning the manner in which urate is excreted by the normal kidney (and the effect of diuresis and various drugs upon its excretion) necessarily subverted the accuracy of most of the earlier studies.

In order to determine the role of the kidney in the pathogenesis of gout it is necessary to select subjects with gout who have not suffered from the disorder long enough to have received significant renal injury from the excessive urates present. If such patients can be found and if their general renal function as indicated by a clearance method is still excellent, accurate measurement of their renal excretion of urate under controlled conditions should furnish an answer to the question of whether there is abnormal renal retention of urate or whether there is excess production of urate in the body of the gouty patient. In the present communication we are reporting such a study of relatively young patients with gout. The results indicate a probable excessive production of urate.

METHODS

Selection of Cases. The diagnosis of gout was determined by clinical and laboratory criteria. Each of the six patients studied had an acute attack of gouty arthritis exhibiting the typical signs and symptoms of the disorder and specifically relieved by colchicine. Two of the six patients had tophi. Each of the patients also had an elevation in plasma urate (6.0 or more mg. per 100 cc.). Although the actual beginning of the disorder could not be ascertained in any of the patients, three of the six were investigated within thirty days after their first clinical eruption of the disorder. None of the patients, however, exhibited signs or symptoms of an acute attack at the time of the study. The average age of the patients was 35 (range: 24 to 42). Thus the study concerned itself with early cases of clinical gout. Sixteen normal subjects and three elderly patients

* From the Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital, San Francisco, Calif. Aided by a grant from the United States Public Health Service.

with chronic gout were selected for control purposes.

Determination of Allantoin and Uric Acid Clearance. The allantoin clearance[4] was used for the determination of the glomerular filtration rate. As stated previously[4] this method has been preferred by us because it does not require intravenous administration of fluids or chemicals. Moreover, the chemical determination of allantoin in biologic fluids is simple and reliable. For the performance of the test the patient was given 10 gm. of allantoin by mouth at 8:00 A.M. At 9:30 A.M. he was catheterized and given 1,000 cc. of water by mouth. At 10:00 A.M. the bladder was emptied, a blood sample taken and the urine collection begun. At 10:45 A.M. a second blood was obtained and the bladder completely emptied. The allantoin and urate content of the two blood and single urine samples were determined according to previously described methods.[4] From the data obtained allantoin clearance (per 1.73 sq.m. of surface area), urate excretion per minute, urate clearance, the ratio of urate excretion/allantoin

TABLE I

THE URATE EXCRETION, URATE CLEARANCE AND ALLANTOIN CLEARANCE IN GOUTY PATIENTS

Case	Age	P.U.[1]	A.C.[2]	U.E.[3]	U.C.[4]	U.E./A.C.[5]	U.C./A.C.[6]
Young Gouty Patients							
R. S.	42	8.7	127.0	1.16	13.3	0.0091	0.1047
O. M.	39	8.3	125.0	1.16	14.0	0.0093	0.1120
C. C.	37	6.5	120.0	1.02	15.8	0.0086	0.1317
E. R.	31	9.8	128.0	1.30	13.3	0.0102	0.1039
A. V.	24	6.7	105.0	0.76	11.4	0.0073	0.1086
Average:	35	8.0	121.0	1.08	13.6	0.0089	0.1122
Old Gouty Patients							
L. C.	70	9.8	78.0	1.51	15.5	0.0194	0.1987
H. F.	67	7.5	72.0	0.76	10.2	0.0165	0.1417
J. D.	66	6.1	77.0	0.55	9.0	0.0072	0.1169
Average:	68	7.8	76.0	0.94	11.6	0.0144	0.1524
Normal Individuals							
W. J.	45	4.9	107.0	0.56	11.3	0.0052	0.1056
W. B.	22	4.7	130.0	0.72	15.1	0.0055	0.1162
G. C.	43	4.0	138.0	0.66	16.6	0.0048	0.1203
F. S.	43	4.4	123.0	0.66	14.8	0.0054	0.1203
D. C.	32	4.6	115.0	0.64	14.0	0.0056	0.1217
C. R.	25	5.0	112.0	0.79	16.0	0.0070	0.1429
F. T.	28	4.6	117.0	0.75	16.4	0.0064	0.1402
R. D.	30	5.1	96.0	0.59	11.6	0.0064	0.1208
D. D.	32	4.0	98.0	0.61	15.1	0.0062	0.1541
A. R.	40	4.7	104.0	0.59	12.6	0.0057	0.1212
Average	34	4.6	114.0	0.66	14.4	0.0058	0.1263

[1] P.U.—plasma urate (mg. per 100 cc.)
[2] A.C.—allantoin clearance (cc. per min. per 1.73 sq.m. of s.a.)
[3] U.E.—urate excretion (mg. per minute)
[4] U.C.—urate clearance (cc. per minute)
[5] U.E./A.C.—urate excretion/allantoin clearance
[6] U.E./A.C.—urate clearance/allantoin clearance

clearance per minute and the ratio of urate clearance/allantoin clearance per minute were calculated.

Determination of the Daily Urate Excretion. The patient was put on a purine-free diet. Twenty-four hours after the diet was started a blood sample was taken and the daily collection of urine was begun. Total twenty-four-hour collections of urine were continued for three to ten days. The initial blood sample and the urine samples were analyzed for urate content. Especial effort was made to ensure an adequate and comparable fluid intake in both patients and controls in order that the effect of oliguria on urate excretion might be obviated.

TABLE II

DAILY EXCRETION OF URATE BY GOUTY PATIENTS ON A PURINE-FREE DIET

Case	Age	Plasma Urate (mg./100 cc.)	Duration of Test (days)	Average Daily Intake, H_2O (cc.)	Average Daily Output, H_2O (cc.)	Average Daily Excretion, Urate (mg.)	Maximal Urinary Concentration, Urate (mg./100 cc.)
Young Gouty Patients							
E. R.	31	9.8	6	2021.0	920.0	601.0	84.0
A. V.	24	6.7	4	1805.0	1800.0	472.0	80.0
O. M.	39	8.3	4	1560.0	1250.0	576.0	53.0
C. C.	37	6.5	3	2050.0	1230.0	613.0	85.0
H. F.	40	7.4	5	1800.0	1640.0	575.0	40.0
Average:	34	7.7	4	1847.0	1368.0	567.0	68.4
Normal Individuals							
W. C.	27	4.2	9	1358.0	945.0	360.0	40.0
O. B.	33	3.8	10	2110.0	2090.0	363.0	22.5
J. D.	23	4.0	9	1860.0	1460.0	390.0	65.0
K. D.	27	3.9	6	1790.0	1230.0	379.0	52.0
H. S.	36	4.8	7	1840.0	1240.0	411.0	50.0
G. P.	30	4.2	4	2600.0	2180.0	438.0	36.5
Average:	29	4.1	8	1926.0	1524.0	390.0	44.3

RESULTS

Allantoin Clearance of the Gouty Patient. In the five young gouty patients tested (Table 1) the glomerular filtration rate was within the range of normal. However, in each of the three old gouty patients (Table 1) the allantoin clearance was sharply reduced, indicating that this particular function of the kidney had been damaged either by the chronic gout, arteriosclerotic disease or a combination of the two.

Urate Excretion and Urate Clearance of the Gouty Patient. When the amount of urate excreted per minute by five young gouty patients was calculated, it was found that they were excreting considerably more urate (Table 1) than the control subjects. Thus the average urate excretion of the five young gouty patients was 1.08 mg. per minute (range: 0.76 to 1.30 mg. per minute) as compared with the excretion rate of 0.66 mg. per minute (range: 0.56 to 0.79 mg. per minute) found in the normal subjects.

Likewise, despite the reduction in their rate of glomerular filtration, the old gouty patients had an average urate excretion (0.94 mg. per minute), 43 per cent greater than that of the average of the control subjects.

The urate clearance, however, of the young gouty patients (Table I) was about the same as that of the controls. There was probably a reduced urate clearance in two of the three old gouty patients.

When the urate clearance of the gouty patients was compared with their glomerular filtration rate (allantoin clearance), it was found (Table I) that the fraction of filtered urate excreted is slightly higher in the normal than in the gouty subjects though perhaps not significantly so. Since the plasma urate is higher in the gouty than in the normal individual, the absolute amount of urate reabsorbed was greater in these patients.

Daily Excretion of Urate in the Young Gouty Individual. As Table II demonstrates, the average daily excretion of urate of five relatively young gouty patients (four of these patients also had been studied previously in respect to their urate and allantoin clearances) on a purine-free diet over an average period of four days was approximately 45 per cent higher than that of the normal individual. It should be mentioned that this disparity was observed on the first day of the diet and continued relatively unchanged throughout the duration of the experiment. This study also indicated that gouty patients had the ability to concentrate urate efficiently. Thus (Table II) maximal concentrations above 75 mg. per cent were observed in one or more twenty-four-hour urine samples of three of the five gouty patients.

COMMENTS

It has long been known that the gouty individual has more urate in his tissues than the normal individual. Since urate is supposedly removed from the body chiefly by renal excretion and also possibly by internal destruction,[3,6] this excessive amount of urate in the tissues of the gouty patient could be caused only by an abnormality in the production of urate or a change in its renal excretion or internal destruction. However, the results of the present research suggest that the relatively young patient subject to acute attacks of gout excretes significantly more urate than the normal individual. Although the present series is a small one, we believe that any gouty patient exhibiting a chronic hyperuricemia will exhibit the same phenomenon. It would appear therefore that when excess parenchymal urate is present in the gouty syndrome, it is due to an overproduction of urate or a failure in its possible destruction.

This conclusion, first suggested in part by Talbott,[5] would have been reached much sooner if earlier investigators had studied the disorder in its earlier stages. Moreover, the usual equivalence of urate clearances in the normal and gouty individual was interpreted by some investigators to indicate that no increased urate excretion occurred in gout. These investigators apparently failed to realize that an unchanged or normal urate clearance in an individual with elevated plasma content of urate (as in the gouty patient) indicates an increase in the actual amount of urate excreted.

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Toxicity of Carinamide*

A Review of 1,997 Patients

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CARINAMIDE, 4′-carboxyphenylmethanesulfonanilide, suppresses the renal excretion of penicillin by the human kidney and elevates the plasma concentrations of penicillin from two to seven times.[1–23] Since the drug is administered for the purpose of inhibiting the function of a transport mechanism of the renal tubules,[24] it is pertinent to inquire whether this end can be accomplished without interference with normal renal functions and without toxicity of such a degree as to prohibit use of the drug. It is the purpose of this paper to review the evidences of toxicity in 1,997 patients to whom carinamide was given.

The diagnoses of the patients included in this report (Table I) indicate that the drug has been given to a representative sample of the patient-population and justify the assumption that the observations of toxicity and lack of toxicity reported are a fair index of what may be expected if carinamide is combined with penicillin in general practice.

Various schedules of dosage of carinamide were employed and the durations of therapy with the compound differed greatly. (Table II.) The drug was injected intravenously to determine the plasma concentrations resulting from various doses and also the rapidity with which the renal excretion of penicillin could be inhibited. Doses of carinamide varying from 3 to 10 Gm. were given in conjunction with oral penicillin for the treatment of acute gonorrheal urethritis in order to evaluate single dose oral therapy.[26] The majority of the 159 patients who received carinamide in a single large dose had gonorrhea. Average amounts of drug, 1.5 to 4 Gm. every three to four hours, were administered for periods of one to fourteen days to 1,694 patients who suffered from the diseases listed in Table I. The ninety-seven patients who received prolonged carinamide therapy, two to seven weeks, had subacute bacterial endocarditis.

The manifestations of toxicity that occurred during carinamide administration are presented in Table III. Some of the symptoms may have been caused by disease (Table I) rather than by the drug; but when in the observer's opinion there was reasonable doubt as to etiology, the symptom was assigned as due to the drug.

SYMPTOMS

General Systemic Symptoms. The symptoms of headache, dizziness, fever, chills, skin rash, erythema nodosum, increased capillary fragility, arthralgia, lymphadenopathy and increase in the size of the salivary glands have all been encountered in cases of drug sensitivity; and although all of these symptoms may not occur in the same patient when several of them appear in combination, there is little reason to doubt that a drug idiosyncrasy exists. Headache and dizziness are so protean that they cannot be ascribed to carinamide with certainty; but when these complaints appeared

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to be unusual in terms of the disease under treatment, they were regarded as being due to carinamide. Fever, chills and skin rash of the scarlatiniform type have occurred together four times and in these four patients[7,22,31] sensitivity to carinamide was demonstrated by recalling the symptoms with a provocative dose of drug. The symptom complex of chills, fever, skin rash and systemic manifestations reappeared within three to eight hours after the ingestion of the test dose. Ten instances of skin rash have been similarly confirmed by provocative administration of the compound but rashes were observed in an additional twenty-three patients that were not proven to be due to carinamide. Penicillin itself causes a variety of skin manifestations and carinamide was given in conjunction with the antibiotic in all of the cases here reported. It was not possible to administer test doses of the two drugs after the subsidence of the skin rashes and the possibility of penicillin having contributed to some of these rashes must be entertained. Nevertheless, all of the thirty-seven cases of skin rash observed in 1,997 patients (Table III) have been ascribed to carinamide.

Increased capillary fragility, increased bleeding time, arthralgia, lymphadenopathy and increase in the size of salivary glands are uncommon signs of drug idiosyncrasy and isolated instances of these manifestations have been observed during treatment with carinamide. One patient showed arthralgia, erythema nodosum, rash and formed elements in the urine during carinamide therapy[15] and the likelihood of this patient having been sensitive to carinamide is very great; but no test dose of carinamide was administered and since penicillin can give all of these signs of toxicity, the responsibility of carinamide in this case is far from being established. However, the observations made in this case have been included in Table III.

Because carinamide contains an $-SO_2-NH-$ group in its chemical structure, it may be chemically classified as a sulfonamide compound. Inspection of the structural formula (Fig. 1) shows, however, that there is no free NH_2- group as there is in a sulfonamide of the sulfanilamide type. Furthermore, carinamide is very resistant to cleavage that would give rise to an aminophenyl containing compound, such as paraaminobenzoic acid. Actually an aluminum-nickel alloy[28] under conditions of vigorous chemical reaction is required to disrupt the carinamide molecule. It is extremely unlikely, therefore, that under physiologic conditions the NH_2- group of carinamide

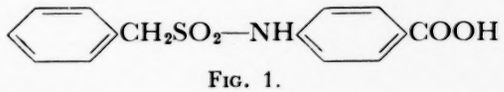

FIG. 1.

TABLE I

DIAGNOSES OF PATIENTS TO WHOM CARINAMIDE HAS BEEN ADMINISTERED

Actinomycosis	Glomerulonephritis	Pyelitis
Arthritis	Gout	Pyelonephritis
Asthma	Impetigo	Sinusitis
Bacteremia	Lung abscess	Streptococcic sore throat
Bronchiectasis	Lymphangiitis	Subacute bacterial endocarditis
Brucellosis	Meningitis	Syphilis
Cholecystitis	Osteomyelitis	Tetanus
Cystitis	Otitis	Tonsillar abscess
Diabetic gangrene	Perianal abscess	Tonsillitis
Diphtheria	Pericarditis	Uremia
Empyema	Peritonitis	Urethritis
Epididymitis	Pneumonia	Vincent's angina
Furunculosis		

TABLE II

DOSAGE AND DURATION OF CARINAMIDE ADMINISTRATION IN 1,997 PATIENTS

Dose	Duration	No. of Patients
Intravenous:		
3-6 Gm.	Single dose	47
Oral:		
3–10 Gm.	Single dose	159
1.5–4 Gm./3–4 hr.	1–14 days	1,694
2–4 Gm./3–4 hr.	14–20 days	56
	21–27 days	14
	28–34 days	17
	35–41 days	1
	42–48 days	4
	49–55 days	3
	56– or more days	2

is reactive. As evidence of this is the fact that carinamide present in large quantities in either plasma or urine cannot be detected by the Bratton-Marshall method of demonstrating a free amino group attached to an aromatic group. It seems unwarranted, therefore, to ascribe the toxic manifestations of carinamide to a relationship in structure between it and the sulfonamide drugs. Carinamide has been administered to patients who were receiving sulfonamide medication and even to a few patients who were known to be sensitive to one or more sulfonamides and no evidences of toxicity or cross-sensitization were observed.

TABLE III
CARINAMIDE TOXICITY IN 1,997 PATIENTS*

Symptom	Numerical Incidence	Percentage Incidence
Headache	5	.25
Dizziness	4	.20
Drug fever	24	1.21
Chills	3	.15
Skin rash	37	1.86
Erythema nodosum	1	.05
Increased capillary fragility	3	.15
Arthralgia	1	.05
Lymphadenopathy	1	.05
Enlargement of salivary glands	1	.05
Increased bleeding time	1	
Anorexia	6	.30
Nausea†	243	12.17
Vomiting	110	5.55
Abdominal cramps (children)	6	.30
Abdominal distention	1	.05
Diarrhea	7	.35
Constipation	2	.10
Backache	3	.15
Costo-vertebral tenderness	1	.05
Urinary frequency	1	.05
Dysuria	2	.10
Oliguria	1	.05
Proteinuria (?)‡	19	.95
Crystalluria	8	.40
Reducing substance in urine	Common	
Formed elements in urine (?)‡	12	.60
NPN elevation	8	.40
Neutropenia (less than 5,000 W.B.C./mm.)	3	.10

* This number of patients represents the total of (1) the cases reported in the available medical literature (cf. bibliography), (2) the author's series of 422 patients not all of whom have been previously reported (cf. bibliography) and (3) those patients treated by other investigators, too numerous to credit individually, who have communicated personally with the authors.

† Because multiple symptoms occurred in some patients, the total number of patients showing toxicity was determined almost entirely by those who were nauseated.

‡ See text for explanation.

Gastrointestinal Symptoms. Anorexia, nausea and vomiting may be considered together as being modalities of the same complaint. The inability, alleged or actual, of many patients to swallow tablets is well known and there is little reason to doubt that the patient's attitude toward repeated large doses of drug may contribute to anorexia, nausea and vomiting. Over and above the patient's attitude, however, is the real difficulty on the part of a cooperative but sick patient to swallow four to eight 0.5 Gm. tablets every three to four hours. Mechanical difficulty in swallowing the large tablets of carinamide is responsible for some of the complaints of nausea and vomiting for it was found that many, but not all, patients who vomited when receiving tablets promptly stopped when the same dose of carinamide was presented in a pleasantly flavored suspension. Crushing the tablets accomplished the same result in many patients. Direct chemical irritation of the gastric mucosa seems unlikely since carinamide is a very mild acid and extremely insoluble in water but this possibility cannot be entirely ruled out. Nausea and vomiting on the basis of toxicity due to accumulation of carinamide in the body have been encountered but excessively high plasma concentrations of carinamide have been tolerated surprisingly well. Although there has been some correlation between nausea and vomiting and carinamide plasma concentrations above 60 mg./100 cc., the highest concentration yet observed (110 mg./100 cc.) was associated with only mild nausea.[5] Contrariwise, some of the most persistent vomiting has been observed in patients whose plasma concentrations of carinamide have not exceeded 20 mg./100 cc. The lack of direct correlation between nausea and vomiting and carinamide plasma concentrations[15] and probable relationship to the number of tablets swallowed[23] has

been confirmed by others. However, some instances of nausea and vomiting may be accounted for on the basis of accumulation of the drug and in these cases the plasma concentrations of carinamide have been greatly in excess of 20 to 40 mg./100 cc., the concentration required for full therapeutic effectiveness.[1,3,4] Accumulation of carinamide occurs in the presence of subclinical renal impairment. Carinamide is excreted by glomerular filtration alone and in the presence of renal disease carinamide will be excreted much less rapidly than by the normal kidney. Even the clinically undiagnosed renal impairment incident to aging of the kidney may contribute to the accumulation of the drug in the circulation and modification of the dosage is required to offset this effect.[18,19,19a] The focal nephritis with predominantly glomerular involvement that is seen in subacute bacterial endocarditis is particularly prone to cause accumulation of carinamide. The fact that carinamide excretion may be influenced by unrecognized renal impairment makes it highly desirable to individualize dosage on the basis of carinamide plasma concentrations.[1,4] The estimation of the compound in body fluids is simple.[28]

Nausea (12.1 per cent) in this series of patients and vomiting (5.5 per cent) proved troublesome enough to preclude the use of carinamide in some patients but by far the majority of these patients in whom nausea was observed were able to continue therapy. The other symptoms referable to the gastrointestinal tract occurred in only a few persons and were so mild that little importance can be assigned to them. Mild abdominal cramps were observed in six children but therapy was not interrupted. Complaints of diarrhea and constipation were so infrequent and so mild that there was real question whether they should be ascribed to the drug.

Genitourinary Symptoms. Backache in three instances and objective costovertebral tenderness, frequency, dysuria and oliguria were observed as isolated symptoms in single patients. In consideration of the fact that active renal infections were being treated with the combination of penicillin and carinamide it seems difficult to assign these symptoms to carinamide alone, but they have been so listed since they appeared at times during which the drug was being administered.

Proteinuria, indicated as having occurred in nineteen patients, has been questioned for the following reasons: Carinamide as a free acid is quite insoluble in water but it is excreted in the urine as the sodium salt or as a conjugate and in either of these forms it is soluble in urine. If the urine is acidified to a pH below 5.0, carinamide is promptly precipitated as the free acid.[4,9,11] Since most of the commonly used tests for proteinuria require acidification of the urine, it is not surprising that carinamide has been precipitated in a heavy cloud and mistakenly interpreted as protein. The crystalline nature of the precipitate is quite obvious; and if the urine be allowed to stand for even a few minutes, it will settle rapidly, much more rapidly than even the heaviest protein precipitate. Acidification with acetic or nitric acids alone seldom precipitates protein; additional denaturing of protein by heating is required. By test it has been demonstrated that when carinamide and protein are present in the same solution, the carinamide can be precipitated by acidification and the supernatant shown to give a protein precipitate only after heating. In addition, it has been demonstrated that the carinamide precipitate can be re-dissolved by the addition of alkali whereas this is not true of protein which has been denatured and precipitated by a combination of acid and heat. Those observers who have been made aware of these facts regarding the testing for protein in urine containing carinamide have confirmed our own observations that the drug does not produce proteinuria but does give rise to confusion in the laboratory because carinamide precipitates upon acidification of urine containing the drug.[6,7,11,16,18,19]

Crystals have been observed in urine that has been cooled by standing at room

temperature but in no instances have hematuria or evidences of mechanical blockage of the urinary tract occurred during carinamide administration. Urine is seldom excreted at a pH as low as 5.0 and it is doubtful whether special measures to alkalinize the urine are necessary, but a daily urinary output in excess of 1,000 cc. should be maintained during carinamide therapy.

Positive tests with Benedict's and Fehling's solutions have frequently been observed following the administration of carinamide.[4,11,14,17] The exact nature of the reducing substance giving this reaction is not known but there is some evidence to indicate that it is a carinamide conjugate, probably the result of conjugation with glycine and /or glucuronic acid. The original suggestion that it was a pentose[17] has not been confirmed and it has not been possible to isolate an osazone.[11] The failure of the substance to be fermented by yeast seems to eliminate the possibility that it is glucose.*

EFFECTS OF CARINAMIDE

Effect of Carinamide on Excretion of Nitrogenous Metabolites. Much interest has centered about the question of whether carinamide interferes with the elimination of the nitrogenous waste products. In no patient with normal renal function to whom carinamide has been administered for periods ranging from a few days to seven weeks has there been any elevation of NPN, uric acid or creatinine in the blood. In man urea is excreted by glomerular filtration and reabsorbed by the renal tubules and carinamide has no influence upon either of these two functions. Endogenous creatinine is likewise excreted only by glomerular filtration and carinamide does not interfere with its excretion. Occasionally an individual with kidney damage excretes creatinine by way of the renal tubules and in such patients carinamide inhibits creatinine excretion.[25] The excretion of uric acid has actually been shown to be increased by carinamide so that it can be said to possess uricosuric properties in common with salicylates.[27] Thus the clinical experience with carinamide that has failed to show interference with the excretion of nitrogenous metabolites[6,10,11,16,18,19,23] is entirely in accord with theory.

Carinamide in Renal Disease. Carinamide therapy should be withheld in the presence of clinical or laboratory evidence of renal impairment, not because carinamide is damaging to the kidneys but because therapy with the drug is usually unnecessary. Tubular dysfunction incident to renal disease results in the elevation and prolongation of penicillin plasma concentrations and there is no need for any additional inhibition of penicillin excretion. Trouble might be anticipated from the administration of carinamide to persons suffering from obvious renal disease because of the rapid accumulation of the drug in the body fluids, but it has been previously noted that tolerance of high plasma concentrations of carinamide is surprisingly good and the only evidences of toxicity from even these high levels have been nausea and vomiting. Despite the lack of need for carinamide in the presence of renal disease the drug has been administered to some uremic patients and it was found that non-protein nitrogen, uric acid and creatinine estimations were not influenced consistently. Slight elevations of the non-protein nitrogen during the administration of carinamide have been observed in twelve patients who were suffering from subacute bacterial endocarditis.[3,9,14] It is well established, however, that in this disease renal impairment is common, involvement of glomeruli being almost a constant feature, and there is frequently progressive deterioration of renal function in the course of the disease. It is difficult, therefore, to determine the role of carinamide in causing retention of urea and creatinine in the presence of subacute bacterial endocarditis, especially since in

* It should be noted that para-aminobenzoic acid does inhibit yeast fermentation (ZARAFONETIS, C. J. D. Para-aminobenzoic acid therapy in scleroderma and lymphoblastoma cutis. Proc. Central Soc. Clin. Research 21: 12–13, 1948) but carinamide does not inhibit yeast fermentation.

man urea and creatinine are excreted by glomerular filtration and carinamide inhibits only a renal tubular excretory transport system.

Histologic Examination of Kidneys after Carinamide. Postmortem examinations of the kidneys of six patients who have received carinamide for extended periods of time prior to death have failed to reveal any evidence of a toxic influence of the drug upon the renal tubules. One patient received carinamide in doses of 24 to 32 Gm. per day, the total dose having been 1,650 Gm. over a period of fifty-eight consecutive days, and the renal tubules were found to be normal.[23] Another received a total of 1,728 Gm. of carinamide during two courses of therapy that totaled sixty days (32 Gm. per day for thirty-one days and 24 Gm. per day for twenty-nine days) and the kidneys failed to show evidence of damage assignable to the drug.[9] This last case was of special interest for the second course of carinamide therapy was begun several weeks after the first course and there was the possibility of having established a drug sensitivity by the initial treatment. This patient failed to show any evidence of sensitization, and sensitization to carinamide has not been observed in over fifty patients who have received the drug on two or more occasions.

Hematologic Toxicity. Mild suppression of the neutrophilic leukocyte count has been observed in two patients. These cases might have been overlooked if pre-carinamide leukocyte counts had not been available that were higher than those observed during therapy. In neither case did the total white count fall below 3,500 or mature polymorphonuclear leukocytes disappear from the blood smears and the white counts rose promptly upon discontinuance of carinamide. In those patients to whom the drug has been administered over the longest periods there has been no evidence of anemia or bone marrow suppression. A single instance of increased bleeding time has been observed that was definitely shown to be due to carinamide sensitivity. It is of interest that this patient showed a normal clotting time, normal prothrombin time and a normal platelet count at the times that bleeding time and capillary fragility were increased.[31]

Effect of Carinamide in Excretion of Other Compounds. Some words of caution about the possible interference of carinamide with the excretion of other drugs seem appropriate. There are tremendous gaps in our knowledge of the exact means by which many commonly employed drugs are excreted by the kidneys, and it is quite possible that many drugs and/or their conjugated products are eliminated by way of the transport mechanism of the renal tubules that is physiologically inhibited by adequate therapy with carinamide. If, therefore, toxic manifestations should occur during carinamide administration, consideration should be given to the possibility that the excretion of some other drug that the patient is receiving is being interfered with by carinamide. Three patients who were on adequate digitalis therapy prior to carinamide therapy rather promptly developed yellow vision and both clinical and electrocardiographic evidences of digitalis intoxication. There were no attendant evidences of interference with renal elimination of fluid balance. The symptoms disappeared following discontinuance of carinamide without alteration in the digitalis therapy. These observations point strongly toward possible interference with the renal excretion of digitalis.

The suppression of the clearance of phenolsulfonphthalein (PSP) during carinamide administration is not an evidence of renal damage[32] but a direct reflection of the effect of carinamide on the renal tubular transport system by way of which phenolsulfonphthalein, diodrast, para-aminohippuric acid, penicillin and other compounds are excreted. Indeed, the PSP test may be employed to regulate carinamide dosage during penicillin therapy.[3,11]

In dogs it has been shown that carinamide does not interfere with the Tm of glucose or arginine, nor with the excretion of sulfa-

diazine, urea or creatinine.[30] In man it has been shown that carinamide elevates the plasma concentration of a number of compounds other than penicillin (to be published W. P. B.), and it is suggested that this effect was produced by reason of inhibition of the renal excretion of the drugs themselves or of various conjugates of the drugs. The action of carinamide in producing inhibition of the renal tubular excretion of drugs other than penicillin may, on the one hand, give rise to unexpected drug toxicity or, on the other, may be taken advantage of to enhance the effectiveness of therapy with agents whose excretion is inhibited.

Chronic Toxicity. It may be observed in Table IV that with few exceptions[9,16,17,22,23,31,33,34] the published reports of the use of carinamide have dealt with results following the administration of the drug for from one to three days. The general lack of toxic manifestations in the reported investigations left unanswered the question of the toxicity that might result from the prolonged administration of the compound. The present review includes ninety-seven patients who have received carinamide in full doses for periods from fourteen to fifty-six days and the almost complete absence of evidences of drug toxicity (with the exception of nausea and vomiting) following prolonged administration should answer, at least in part, the questions concerning chronic toxicity in humans, particularly with reference to the likelihood of the drug producing renal impairment. To date there is no convincing evidence that carinamide is nephrotoxic.

In the original publication on the use of carinamide to enhance penicillin plasma concentrations it was stated that the toxicity of the drug was of a low order, but since the number of patients reported was small a qualifying statement was made " . . . in the course of extended clinical experience with carinamide it is unlikely that some type of sensitivity or toxic manifestations will fail to be observed."[8] As noted in this present paper, thirty-seven patients have shown typical drug reactions to carinamide and nausea and vomiting have occurred frequently, but observations in nearly 2,000 patients supports the originally expressed opinion that carinamide possesses a low order of toxicity.

SUMMARY

A review of 1,997 patients to whom carinamide was administered has demonstrated that the drug possesses a low order of toxicity. Exclusive of nausea (12.1 per cent) and vomiting (5.5 per cent) the incidence of toxic manifestations was less than 2 per cent. True drug sensitivity was confirmed in fourteen patients and may be assumed in twenty-three additional cases although the concurrent administration of penicillin raises some questions as to the etiologic role of carinamide in all of the latter cases. Nausea may preclude therapy with the drug but this symptom may in large measure be ascribed to the mechanical factor of swallowing a large and oft-repeated dose of drug rather than to toxicity of the drug itself. From the observations recorded there is no indication that carinamide interfered with the elimination of normal nitrogenous metabolites or permanently impaired renal functions. Carinamide should be withheld in the presence of renal disease not because it is damaging to the kidneys but because its administration is unnecessary. Since carinamide is excreted almost entirely by glomerular filtration and subclinical grades of renal impairment cause accumulation of the drug in the circulation, dosage should be individualized and controlled by plasma carinamide estimations. It is possible that carinamide, by exerting its pharmacologic action upon the renal tubules, may inhibit the tubular excretion of some commonly employed medications. Few drugs in common use, even those that are granted to have little or no toxicity, can be given in the large doses, 18 to 32 Gm. per day, over periods of time up to sixty days, that are recorded here for carinamide.

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Congenital Thrombocytopenic Purpura*

Purpura Hemorrhagica in Pregnancy and in the Newborn

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THE association of purpura with pregnancy has been reported often since the original description by Barnes[1] in 1867 but there have been relatively few instances in which the clinical and hematologic data of both mother and child have been fully presented. Consequently confusion has arisen in classifying the purpura present in the mother and in determining the effects of the disease on the child. During the past ten years the authors have followed five patients with purpura hemorrhagica through seven pregnancies. The information obtained is presented in this communication as an aid in evaluating the prognosis of purpura hemorrhagica in pregnancy and as a contribution to understanding the pathologic physiology of the condition.

METHODS

Platelet counts were performed by a modification[2] of the Rees-Ecker technic[3] on capillary or venous blood. Duke's method[4] of determining the bleeding time was employed. Pohle and Taylor's modification[5] of the Lee-White technic[6] was used for measuring coagulation times and the clot retraction was observed after one, two, four and twenty-four hours' incubation at 37.5°C. Capillary fragility was measured by maintaining a blood pressure cuff, inflated to 100 mm. Hg, on the upper arm for seven to ten minutes. In this laboratory the following ranges of normal variation have been obtained for the above mentioned procedures: platelet count, 150,000 to 400,000 per cu. mm.; bleeding time, one to four minutes; coagulation time, six to twelve minutes; clot retraction, complete in four hours; tourniquet test, occasionally a few scattered petechiae present distal to the blood pressure cuff after inflation for ten minutes. Studies of the bone marrow were made on material aspirated from the sternum with a Turkel needle,[7] spread thinly and air dried on glass slides, and later stained with Wright's stain.

RESULTS

The full case reports are presented in detail later. Significant data obtained from the mothers and children are presented in Table I. In all instances the mothers suffered from typical purpura hemorrhagica (Werlhof). The age of onset of the purpura varied from three to twenty-eight years; in the last instance the first symptoms of purpura preceded pregnancy by only a few months. In all of the patients the platelet counts were low. The bleeding times were generally prolonged, the clot retractions poor and the tourniquet tests positive. With the exception of purpuric phenomena the patients' past histories were unimportant.

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In none was there a previous family history of purpura.

Three of the patients had their spleens removed with at least a temporary rise of the blood platelet count to normal or above and disappearance of the purpura. Splenectomy was performed in one patient (H. H.) during the sixth month of pregnancy because of severe epistaxis. The postoperative course was uncomplicated, the epistaxis ceased and the blood platelet count rose to normal. Following splenectomy two of the patients (H. H. and G. S.) have maintained normal platelet counts and have not had purpura for periods of two and three years, respectively. The interval since splenectomy has been thirteen years for the other patient (R. P.) and she has had recurrence of thrombocytopenia and of purpura.

During the period of study seven children were born to this group of five women. Three were females and four were males. Six had blood platelet counts below 100,000 per cu. mm. at or shortly after birth. Purpura, generally mild, but with severe melena in one instance, was observed in five of the children. It was not always possible to follow the blood platelet counts of the

TABLE I

SUMMARY OF DATA OF MOTHERS AND CHILDREN (AUTHORS' CASES)

Patient and Present Age	Age of Onset of Hemorrhagic Symptoms	Age of Diagnosis of Purpura Hemorrhagica	Laboratory Data	Age at Splenectomy	Course after Splenectomy	Pregnancies				
						Mother	Child			
						Age	Sex of Child	Laboratory Data	Hemorrhagic Symptoms	Duration of Thrombocytopenia
1. R.P. 25	3	12	Pl.C.* 64,000 B.T.† 12 min. T.T.‡ positive C.R.§ poor	12	Recurrence of thrombocytopenia and purpura in 3 years	17	♂	1 day postpartum Pl.C.* 8,000 B.T.† >20 min.	Gastrointestinal tract bleeding	2½ months
						18	♂	1 day postpartum Pl.C.* 11,000 B.T.† 10 min.	Petechiae; gastrointestinal tract bleeding	3¾ months
						23	♂	1 day postpartum Pl.C.* 13,000 B.T.† >10 min.	Petechiae; gastrointestinal tract bleeding	3½ months
2. V. B. C. 34	24	25	P.C.* 55,000 B.T.† >10 min. T.T.‡ weakly positive C.R.§ none	Not performed	.....	33	♀	4 days postpartum Pl.C.* 188,000 B.T.† 4½ min.	Few petechiae	Pl.C.* 304,000 on 7th postpartum day
3. W. C. 30	28	28	Pl.C.* 7,000 B.T.† 13 min. T.T.‡ positive C.R.§ none	Not performed	.....	28	♀	4 weeks postpartum Pl.C.* 63,000 B.T.† 4½ min.	None	2 months
4. H. H. 27	10	22	Pl.C.* 26,000 B.T.† 4 min. T.T.‡ positive C.R.§ none	22, at 6th month of pregnancy	Platelet counts normal; no symptoms	22	♂	1 day postpartum Pl.C.* 13,000 B.T.† prolonged	Petechiae; ecchymoses, gastrointestinal tract bleeding	Pl.C.* at 2 years 223,000
5. G. S. 29	22	24	Pl.C.* 30,000	24	Platelet counts normal; no symptoms	26	♀	1 week postpartum Pl.C.* "almost absent" (<100,000)	None	"Normal" by 12 months

* = platelet count per cu. mm.
† = bleeding time
‡ = tourniquet test
§ = clot retraction

infants at regular intervals, but in all instances the platelet counts* became normal within two years, in five within two to four months after birth. Purpura likewise disappeared. There were no other abnormalities observed in the children at birth and subsequently all developed normally.

Even though there were few platelets circulating in the blood of most of these children they had few hemorrhagic episodes and none required transfusion therapy. Thrombocytopenia occurred in the children irrespective of their sex and whether they were fed at breast or by bottle. There was no relationship of the age, parity or presence or absence of the maternal spleen to the syndrome in the child. There was, however, a rough correlation between the severity of the disease in the mother and in the child. For example, R. P. (Case I) and H. H. (Case IV), whose symptoms were severe clinically, bore children who had thrombocytopenia for a longer period of time and had more of a hemorrhagic diathesis than the children of V. B. C. (Case II) and W. C. (Case III) whose symptoms were of moderate severity.

In none of the three mothers in whom purpura hemorrhagica was known before pregnancy were the purpuric manifestations accentuated by the pregnancies. None experienced complications during labor, at delivery or in the puerperium. Two of these individuals, R. P. and W. C. (Cases I and III), at times when their platelets were diminished, were subjected to major surgical procedures without the occurrence of abnormal bleeding. An episiotomy was performed on a third, V. B. C. (Case II), without unusual bleeding or retardation of healing.

COMMENT

A review of the literature reveals that in instances in which it has been possible to study the status of a child born of a woman with purpura hemorrhagica, evidence of congenital thrombocytopenic purpura has usually but not invariably been found during a short period following birth. Data summarized from the literature regarding the initial platelet counts and duration of thrombocytopenic purpura in the children are presented in Tables II and III. Congenital thrombocytopenic purpura occurred whether or not the spleen of the mother had been removed prior to or during the pregnancy, as shown in Table IV.

TABLE II
INITIAL PLATELET COUNTS IN CHILDREN
(ALL REPORTED CASES)

Platelet Counts in Thousands	Children No.	Per cent
0–50	14	30.2
50–100	4	8.8
100–150	2	4.4
150 plus	3	6.6
Insufficient data or child born dead	23	50.0
Total	46	100

TABLE III
DURATION OF THROMBOCYTOPENIA IN CHILDREN
(ALL REPORTED CASES)

Days	Children No.	Per cent
0–10	4	8.3
10–30	2	4.1
30–60	5	10.3
60–90	3	6.2
90–120	2	4.1
120 plus	1	2.0
Insufficient data or child born dead	29	(65.0)
Total	46	100

TABLE IV
EFFECT OF MATERNAL SPLENECTOMY ON THROMBOCYTOPENIC PURPURA IN CHILDREN
(ALL REPORTED CASES)

Maternal Splenectomy Performed	17	(36.9%)
Thrombocytopenic purpura present in child	15	(88.2%)
Thrombocytopenic purpura absent in child	2	(11.8%)
Maternal Splenectomy not Performed	8	(17.4%)
Thrombocytopenic purpura present in child	6	(75.0%)
Thrombocytopenic purpura absent in child	2	(25.0%)
Insufficient data or child born dead	21	(45.6%)
Total	46	(99.9%)

Cases have been described by Waltner,[8] Liebling,[9] Sanford, Leslie and Crane,[10]

* In one instance (the child of G. S.) direct platelet counts could not be done but blood smears were examined.

Morrison and Samwick,[11] and Patterson[12] in which maternal splenectomy was *not* performed. In each instance both mother and child survived. Morrison and Samwick obtained an aspirated specimen of bone marrow fluid from the child they studied and found an increased number of megakaryocytes. In a similar group of patients reported by Ohnesorge,[13] Rossi,[14] Tesauro[15] and De Saussure and Townsend[16] the infants were born dead. The status of the children described by Hottenstein and Klingman,[17] Breda[18] and Siegler[19] is not clear. Wintrobe[20] mentions four patients with purpura hemorrhagica who became pregnant. Two of these patients died and of the other two who were delivered, one had a child with thrombocytopenia but bleeding did not occur. Presumably the other child did not have depressed platelet counts.

When splenectomy has been performed *prior to* the onset of pregnancy, congenital thrombocytopenic purpura has been noted in the children. The mother and child described by L. T. Davidson[21] had favorable outcomes as did the three children born of Talmadge and Berman's[22] patient and one of Urbanski and Hunter.[23] Both of the children delivered of one of Finn's[24] patients had evidence of purpura, although in one instance the platelet count was 120,000 per cu. mm. This child died and at autopsy many hemorrhagic areas were found in the brain, viscera and subcutaneous tissues. Study of the aspirated sternal marrow fluid of the second child revealed a decreased number of megakaryocytes and apparent failure of platelet production. However, this child recovered with transfusion therapy. The patient of Whitney and Barritt[25] had two children who died seventy-two and twenty-four hours postpartum, respectively, with petechiae, ecchymoses and thrombocytopenia. Examination of bone marrow obtained at autopsy revealed normal megakaryocytes in the first child while in the second only a few immature cells of this series were seen. Brown and Elliott[26] mention one patient who did not respond well to splenectomy, continuing to have moderately severe purpura for eight and one-half years. After the pregnancy all bleeding symptoms ceased although the platelet count remained low. Following splenectomy of another of their patients a child was born with the classical signs and symptoms of thrombocytopenic purpura.

Phythyon and Lartz[27] described a patient who had a splenectomy at the eighth month of pregnancy. Four days later a macerated fetus was delivered. Grossman[28] briefly mentions a patient whose spleen was removed during the fifth month of pregnancy but the results of this procedure on both the mother and fetus are not reported.

Instances have been reported in the literature of the mother presumably having purpura hemorrhagica without apparent thrombocytopenia occurring in the child. The platelet counts of the patient described by Burnett and Klass[29] increased spontaneously from 15,000 to 163,000 per cu. mm. during the last two trimesters, indicating that a partial spontaneous remission might have occurred. However, at the time of delivery the mother's platelet count had decreased to 76,000 per cu. mm. The platelet count of the child at birth was greater than 121,000 and increased to 332,000 per cu. mm. on the seventh postpartum day. Finn[24] reported the case of a negress whose spleen was removed three years before pregnancy and whose child had no clinical or laboratory evidence of thrombocytopenic purpura. A splenectomy was performed after five and one-half months of pregnancy in the patient described by Bernstein, Newman and Hitzig.[30] The child, who had a platelet count of 170,000 per cu. mm., died of pulmonary atelectasis on the eighth postpartum day. Patients described by Hottenstein and Klingman,[17] Barbera,[31] Troland and Lee[32] and Limarzi[33] either did not have splenectomies before or during the pregnancy, or the spleen was removed after delivery. Detailed laboratory data of the child were not presented in any of these reports.

In addition to the case reports mentioned

above Barclay,[34] Schefrin and Shechtman[35] and Waters[36] have described recently born infants with thrombocytopenic purpura born of apparently normal mothers. After periods of time varying from nine days to six months the platelet counts spontaneously increased to normal values. Greenwald and Sherman[37] gave no information about the mother but describe severe thrombocytopenic purpura in a six day old infant. Death subsequently occurred and at autopsy there were found congenital heart disease, an anomoly of the thymus gland and megakaryocytes in the bone marrow which were decreased in number as well as altered morphologically.

Posner's[38] patient was sensitive to quinine which was used to induce labor. The mother had thrombocytopenic purpura as did the child for sixteen days postpartum. The patient of Peshkin and Miller[39] was also sensitive to quinine and ergot but apparently did not develop severe thrombocytopenia. Unfortunately no information about the child is given. One of McGoogan's[40] two patients was receiving antiluetic therapy until shortly before the onset of the hemorrhagic diathesis. Platelet counts were not performed before delivery and blood transfusion, although the bleeding time was prolonged and the clot retraction delayed. The other case did not develop thrombocytopenia; both mothers were delivered of dead infants. Bleeding in Israel and Winson's[41] patient was coincident with hyperemesis gravidarum and thyrotoxicosis, but thrombocytopenia did not occur. Two macerated fetuses and one child that lived for three hours were born; at autopsy areas of cerebral hemorrhage were found in each.

Several cases of thrombocytopenic purpura coexisting with other diseases have been reported. The platelet counts of Rodecurt's[42] patient, who had pyelitis, cystitis and hypocalcemia, increased dramatically on the ninth postpartum day. The child also had a somewhat depressed platelet count as well as hypocalcemia. Thrombocytopenic purpura associated with "agnogenic myeloid metaplasia,"[43] Boeck's sarcoid of the spleen[44] and eclampsia[45] have been reported in the mothers without apparent abnormality in the children.

So little information is presented by Barnes,[1] Byrne,[46] Rowe,[47] Mosher[48] and Rushmore[49] that their cases cannot be properly evaluated.

TABLE V
NUMBER OF PREGNANCIES COMPLICATED BY PURPURA HEMORRHAGICA (ALL REPORTED CASES)

	No.	Per cent
Mothers		
Living	42	91.3
Dead	4	8.7
Total	46	100.0
Children		
Living	34	73.9
With purpura	19	55.9
Without purpura	10	29.4
Insufficient data	5	14.7
Dead	12	26.1
With purpura	1	8.3
Without purpura	2	16.6
Born living, but died in 1–3 days with purpuric manifestations	3	24.9
Therapeutic abortion	1	8.3
Insufficient data	5	41.5
Total	46	100.0

The data obtained in our small series are in general agreement with the well documented cases reported in the literature. Including our series, we have been able to find forty-six reported pregnancies in women who apparently had purpura hemorrhagica. (Table v.) Of these pregnancies 8.7 per cent ended fatally for the mother, while 26.1 per cent of the children were either born dead or died within three days postpartum. However, only one-third (33.2 per cent) of the fatalities had definite evidence of thrombocytopenic purpura. Of the children 73.9 per cent were born living and of these approximately one-half (55.9 per cent) had purpuric manifestations. Probably more children born of mothers with purpura hemorrhagica have congenital thrombocytopenic purpura than these figures indicate. Information, especially laboratory data, relative to the child has often been incomplete. More detailed observations most likely would have revealed charac-

teristics of this syndrome in a larger number of instances.

The disease in the child is self-limited. No relapses have occurred in our patients who have been followed for from ten months to eight years although, in the child of Patterson's[12] patient, the platelet count had decreased from 175,000 per cu. mm. at seventy-five days to 95,000 per cu. mm. at the end of a year. Treatment should be directed to support the infant through the acute episode until spontaneous remission occurs. If anemia due to blood loss has occurred, depending upon the urgency of the situation, orally administered iron or transfusions should be given.

The occurrence of thrombocytopenic purpura in children born of women with purpura hemorrhagica is of interest in view of the current discussion of the pathologic physiology of the disease. Frank[50] advanced the theory that the thrombocytopenia is due to an inhibition of bone marrow megakaryocyte activity by an agent produced in the spleen. Troland and Lee[32] injected into laboratory animals extracts of spleens removed from patients with purpura hemorrhagica and observed a transient thrombocytopenia. However, this work has not been widely confirmed.[51,52] More recently Limarzi and Schleicher[53] and Dameshek and Miller[54] have demonstrated a hyperplasia of bone marrow megakaryocytes with diminished numbers of these cells apparently producing platelets. The latter authors found that following splenectomy a dramatic increased occurred in the number of megakaryocytes that appeared to form platelets.[54]

Kaznelson's[55] theory of the etiology of purpura hemorrhagica is that the platelets are formed in at least normal numbers in the bone marrow but that they are phagocytosed and destroyed in increased numbers in the spleen. The work of Wiseman and his co-workers[56] supports this hypothesis.

The experimental studies of Bedson[57,58] have given rise to a third theory. By injecting an agar-serum mixture intravenously into dogs he was able to produce thrombocytopenia, but purpura did not occur unless the capillary endothelium had been previously damaged by the injection of an anti-red cell serum. Thus it appeared that the primary defect might be in the capillaries and that the platelets were being utilized in an attempt to maintain the endothelial integrity.[59]

It is not known which of these three hypotheses is correct. However, hyperplasia of marrow megakaryocytes apparently exhibiting at the same time decreased platelet formation and the occurrence of thrombocytopenic purpura in infants whose mothers have purpura hemorrhagica is strong circumstantial evidence in favor of Frank's theory. Thus it seems that some agent that depresses platelet formation might be transferred across the placenta into the fetal circulation. This agent might be an immune body or a hormone. In a study of purpura following estrogen therapy Watson, Schultz and Wikoff[60] suggested the possibility of a causal relationship between stilbestrol and other estrogens and purpura. At least three of their five patients had evidence of hypersensitivity to estrogen by skin testing. Hormone or not, it is apparent that the material thought to be transferred across the placental membrane is present in the mother quite independent of the simultaneous presence or absence of the spleen. Some of the results of the bone marrow studies of infants with congenital thrombopenic purpura are consistent with the presence of a substance transmitted from the mother across the placental membrane but certainly more data are needed.

CASE REPORTS

CASE 1. Mrs. R. P. was a twenty-five year old white American housewife of Italian descent. Since the age of three years it was noticed that she "bruised easily" and frequently a red, punctate "rash" would appear spontaneously on her neck and trunk. At the age of nine, following tonsillectomy and adenoidectomy, a profuse hemorrhage occurred from the operative site necessitating repeated transfusions. The menarche at twelve was followed by a ten-day interval of severe menorrhagia. She was

first seen at the Thorndike Memorial Laboratory at this time. The past, family and social histories were non-contributory. Physical examination was not remarkable aside from symptoms and signs of moderately severe shock. The pertinent laboratory data on admission was as follows: "Gross examination: Specimen consists of a deep, purple-red, firm spleen measuring 10 × 7 × 3 cm. and weighing 175 gm. The capsule is smooth and glistening. The cut surface is deep purple-red and the follicles and trabeculae are prominent. Little can be scraped

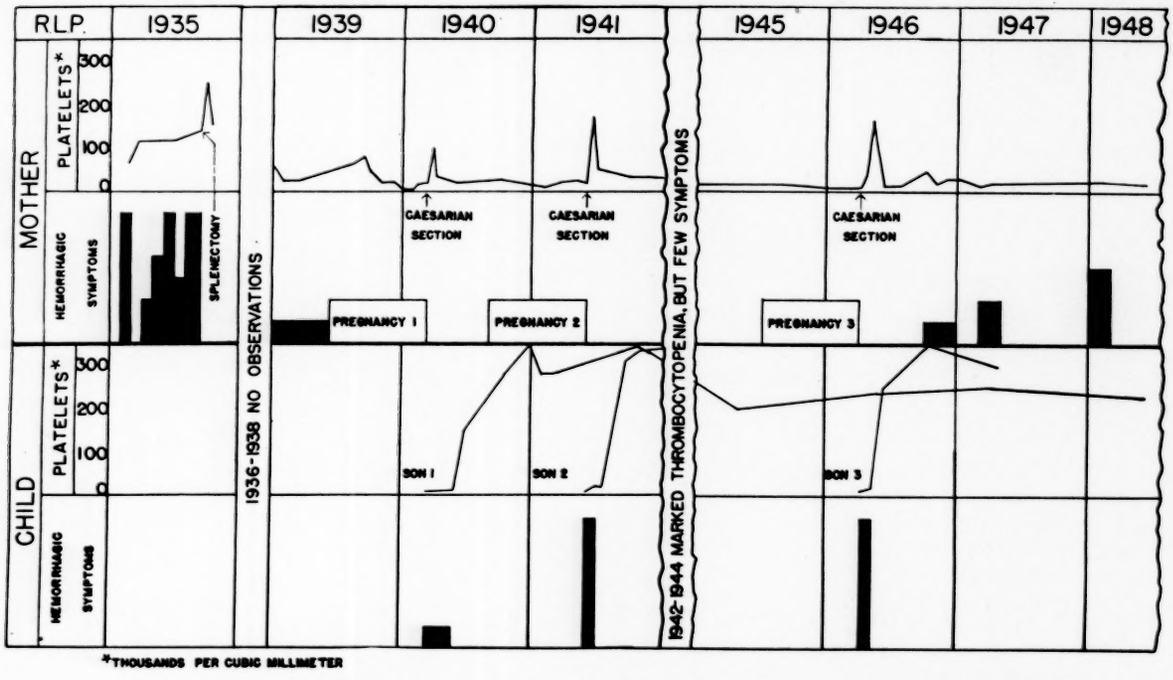

FIG. 1. Case 1. Clinical course and blood platelet counts of mother and children.

were: platelets almost completely absent on the smear; subsequently a count of 64,000 per cu. mm. was obtained. The bleeding time was twelve minutes, the coagulation time twelve minutes, clot retraction poor in twenty-four hours and the tourniquet test positive. Following two transfusions of 500 cc. of whole blood the bleeding ceased and with the oral administration of iron the erythrocyte count and hemoglobin level rapidly rose to normal. During the following three months there was no vaginal bleeding but the skin manifestations of purpura persisted. Platelet counts varied between 75,000 and 122,000 per cu. mm. (Fig. 1), the bleeding time remained prolonged, the clot retraction poor and the tourniquet test positive. Profuse menorrhagia accompanied the second menstrual period and upon hospitalization the physical findings and laboratory data were essentially the same as on her first admission. Dietary therapy and a course of x-ray irradiation over the spleen did not prove to be beneficial. Splenectomy was therefore performed on September 18, 1945. The pathologist's report from the cut surface. Microscopic examination: There is a toxic reaction in some of Malpighian corpuscles. The pulp is congested. No megakarycocytes are seen."

Following splenectomy the patient was greatly improved. All of the laboratory findings became normal, the skin lesions did not recur and the menses subsequently became regular without menorrhagia. At no time was there metrorrhagia.

At the age of fifteen the patient was married. Seven months later, after a six-week period of amenorrhea, menorrhagia recurred accompanied by cramping lower abdominal pains. Physical examination at this time was not contributory. The platelet count was 73,000 per cu. mm., the bleeding time six and one-half minutes, the clot retraction poor in twenty-four hours and the tourniquet test negative. Bleeding ceased spontaneously after forty-eight hours. No fetal tissue was identified.

When seventeen years old the patient became pregnant for the first time. Except for a few petechiae about the ankles there was no abnormal bleeding during the pregnancy although

the platelet counts varied between 4,000 and 81,000 per cu. mm. Because of a generally contracted pelvis an obstetrical consultant advised and performed a low cesarean section at term. The amount of blood lost at operation was not excessive and the convalescence was uneventful. Two subsequent pregnancies occurred at the ages of eighteen and twenty-three years and both children were also delivered by cesarean section without untoward incidents. At the third operation sterilization was accomplished by extirpation of the Fallopian tubes.

All three of the infants were males, weighed between 6 pounds 5 ounces and 8 pounds 6 ounces and aside from bleeding manifestations were normal in every respect. The eldest son was nursed at breast, supplemented by bottle feedings for three months, while the two younger sons were bottle fed from birth. The first child showed no evidence of purpura although at birth his platelet count was 8,000 per cu. mm. and his bleeding time was greater than twenty minutes. One episode of mild gastrointestinal bleeding occurred at the age of six weeks but transfusions were not required. At the age of two and one-half months the platelet counts and bleeding times spontaneously returned to and have subsequently remained at normal levels. The second child had petechial hemorrhages on the skin of the face and chest at birth and on the third postpartum day the stools were heavily streaked with blood. The bleeding time initially was greater than ten minutes and the platelet count 11,000 per cu. mm. Clinical evidence of bleeding ceased on the twenty-sixth postpartum day without treatment although the platelet counts remained greatly depressed until the age of three and three-fourths months, at which time they rapidly rose to normal levels. The third child had a few petechiae on the face and body at birth. They reached a maximal number on the third postpartum day and then gradually disappeared during the following week. Tests for occult blood in the stools were strongly positive from the second to the seventh postpartum day. At birth the platelet count was 13,000 per cu. mm. and the bleeding time greater than ten minutes. The platelet counts remained greatly depressed for the initial three and one-half months of life after which they increased to normal.

CASE II. Mrs. V. B. C. was a thirty-four year old white registered nurse of combined French-German-English descent. Her menses had always been regular every twenty-eight to thirty days, lasting four or five days until the age of twenty-four when she experienced a six-week episode of menorrhagia. Subsequently her periods occurred every twenty-one days and persisted from seven to nine days, with an excessive flow. On one occasion shortly before being seen at the Thorndike Memorial Laboratory, the patient observed scattered ecchymoses immediately prior to and following menstruation. Oozing from the gums occurred at infrequent intervals, stopping spontaneously after approximately ten minutes. A review of the past, family and social histories was not otherwise remarkable aside from the fact that her mother had pernicious anemia. The physical examination revealed only moderate obesity, a few fading ecchymoses on the upper thighs and dental caries. Laboratory studies showed a platelet count of 55,000 per cu. mm., bleeding time of greater than ten minutes, coagulation time of seven minutes, poor clot retraction in twenty-four hours and a weakly positive tourniquet test. Initially the patient was treated symptomatically and at various times during the ensuing years different therapeutic regimens were tried without objective improvement. At the age of thirty-three the patient became pregnant. The pregnancy was uneventful aside from a few scattered petechiae and ecchymoses and an occasional brief episode of gum bleeding. The platelet counts varied between 44,000 and 100,000 per cu. mm. (Fig. 2), the bleeding times between three and one-half and six and one-half minutes, the tourniquet tests were moderately positive and the clot retractions were slightly diminished. The coagulation and prothrombin times were normal. Labor began spontaneously at term and after a three-hour period of labor an episiotomy was performed and a 6 pound 8 ounce girl was born. Unfortunately the child was not seen by us until the fourth postpartum day. At that time she had a small petechial hemorrhage on the abdomen but otherwise showed no hemorrhagic stigmata. The platelet count was 188,000 per cu. mm., the bleeding time four and one-half minutes, coagulation time six minutes, with normal clot retraction in four hours. The platelet count increased to 304,000 per cu. mm. on the seventh postpartum day at which time the mother and child were discharged from the hospital. They have not returned for follow-up studies.

Case III. Mrs. W. C. was a thirty year old white housewife of Italian lineage. She was entirely asymptomatic until the age of twenty-eight when she first noticed petechiae about the ankles and lower portions of the legs. Shortly thereafter ecchymoses appeared spontaneously

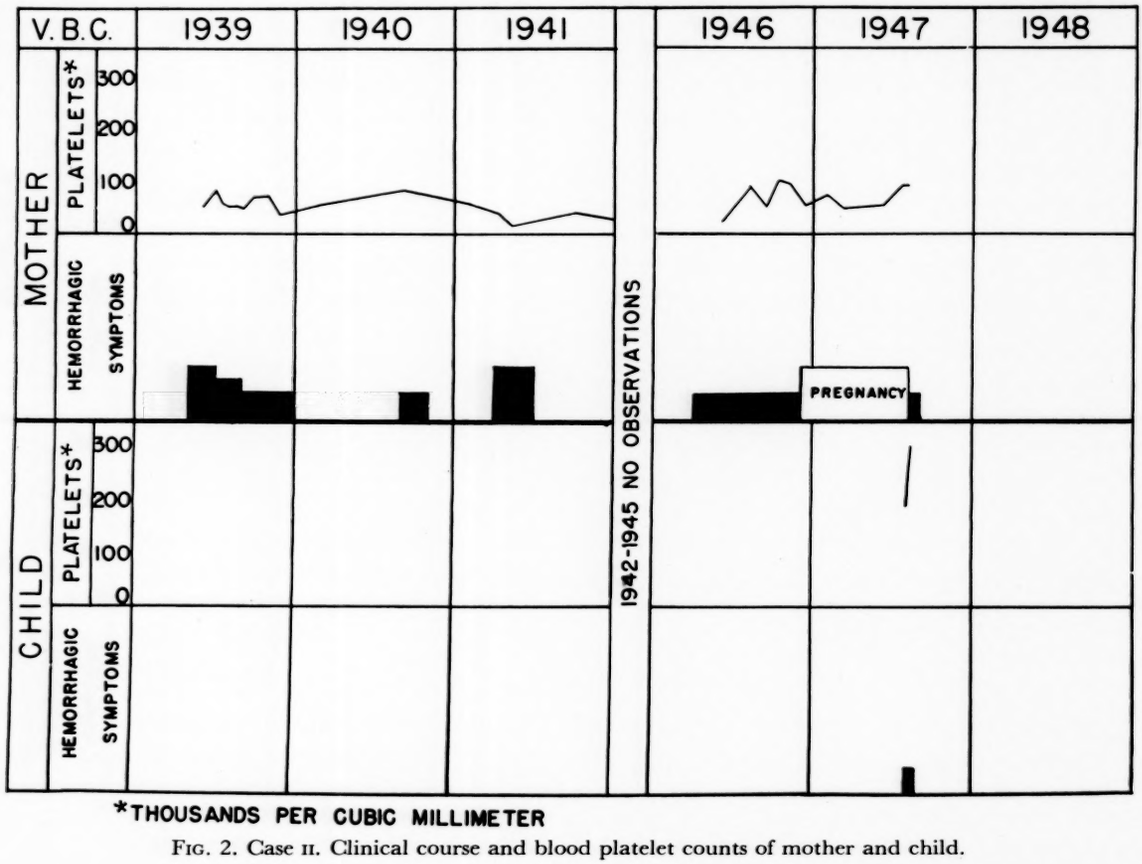

Fig. 2. Case II. Clinical course and blood platelet counts of mother and child.

on the lower abdomen and thighs and she had a mild epistaxis from the left nostril. She was hospitalized elsewhere and the epistaxis was controlled with thrombin and fibrin foam packs and a transfusion of 500 cc. of whole blood. The diagnosis of purpura hemorrhagica was made when repeated examinations of the blood revealed practically no platelets. She was then transferred to the Thorndike Memorial Laboratory for further diagnostic procedures and treatment. She had had two normal pregnancies and deliveries at the ages of twenty-three and twenty-five and one-half years. The past and family histories were not remarkable. Except for the presence of numerous petechiae, especially about the ankles, and several scattered ecchymoses, the physical examination was noncontributory. Pertinent laboratory data were: platelet count 7,000 per cu. mm., bleeding time thirteen minutes, no clot retraction in twenty-four hours and a strongly positive tourniquet test. The prothrombin and coagulation times were normal. Many of the platelets seen on blood films were very large and basophilic when stained with Wright's stain. Aspirated marrow fluid revealed an increased number of morphologically unaltered megakaryocytes demonstrating apparently diminished platelet production. There was no increase in the number of eosinophiles when counted by the technic described by Schwartz.[61] The patient was treated symptomatically and, except for mild skin manifestations of purpura, was asymptomatic for six weeks although her platelet counts remained greatly depressed. (Fig. 3.) At this time she developed pain in the right lower quadrant of the abdomen. A laparotomy performed elsewhere revealed a "follicle cyst hematoma" of the right ovary. A right oophorectomy and appendectomy were performed without operative or postoperative complications. Approximately two months later she became pregnant for the third time. The pregnancy was uneventful aside from the occasional appearance of

scattered petechiae and ecchymoses on the lower extremities. At term a normal female child weighing 6 pounds 12 ounces was delivered at another hospital after a "short uneventful labor." There was little bleeding at delivery and during the puerperium. Apparently there were few purpuric manifestations present in the child at birth. The child was breast fed for five months without supplemental milk feedings. When first seen at the Thorndike Memorial Laboratory at the age of four weeks, a history of abnormal bleeding in the infant could not be obtained and the physical examination revealed no abnormality. The platelet count was 63,000 and the bleeding time four and one-half minutes. At eight weeks the platelet count had risen to normal and has since remained at this level.

Case IV. Mrs. H. H. was a twenty-seven year old white housewife of Germanic ancestry. From the age of ten years she had frequent epistaxes and bruised easily. The epistaxes were always precipitated by slight trauma, e.g., sneezing, blowing or hitting the nose, or by an upper respiratory infection. The menarche was at sixteen years; the menses were regular every twenty-eight to thirty days but she flowed profusely for a week, saturating eight pads daily. Occasional epistaxes were associated with menstruation. At the age of twenty-two the patient became pregnant. The pregnancy was uneventful except for epistaxes occurring regularly at monthly intervals corresponding to the time of her expected menstrual period. After approximately thirty minutes of rest and the local application of cold compresses the epistaxes usually ceased. At the sixth month of pregnancy she experienced two episodes of massive nasal bleeding and because of failure to obtain relief at home, she was admitted to the Thorndike Memorial Laboratory. The past, family and social histories revealed no significant information. In particular, there had been no rheumatic diathesis or petechiae. The physical examination was not remarkable aside from small ecchymoses scattered over the lower extremities and a symmetrically enlarged uterus compatible with a pregnancy of six months. Pertinent laboratory data were: platelet count 26,000 per cu. mm., bleeding time four minutes, coagulation time seven minutes, clot retraction very slight in twenty-four hours and tourniquet test strongly positive. On blood smear the platelets were found to be enlarged. The prothrombin time was normal. The patient was repeatedly transfused in order to compensate for her severe blood loss and the epistaxes were controlled with thrombin packs. During the following six weeks she had four additional episodes of bleeding from the nose, two severe and two moderately severe. Therefore, after

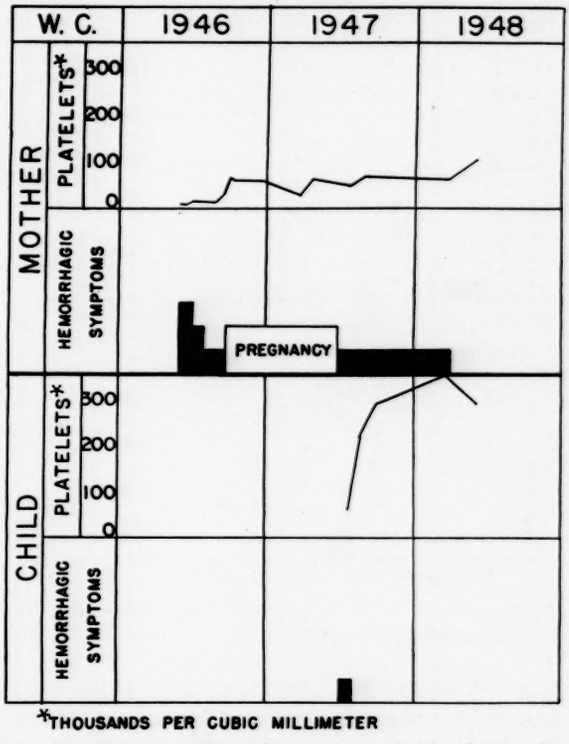

Fig. 3. Case III. Clinical course and blood platelet counts of mother and child.

several preoperative transfusions a splenectomy was performed with uneventful recovery. The pathologist's report was: "Gross examination: Specimen consists of 2 slices of spleen including the capsule, measuring approximately 4 × 3 × 0.5 cm., received in Zenker's solution. Microscopic examination: Consistent with thrombocytopenic purpura." Her postoperative convalescence was uninterrupted. The platelet count rose to normal on the fourth postoperative day (Fig. 4) and bleeding did not recur. At term a 7 pound 10 ounce boy was delivered with low forceps. Physical examination of the child revealed no abnormality aside from a 1½ cm. hematoma on each cheek and a single petechial hemorrhage on the left leg. The baby was bottle fed from birth. Subsequently, ecchymoses developed about the sites of skin punctures and intravascular injections of medication; petechiae appeared on the hard palate where it was in contact with the rubber nipple,

and one stool was guaiac positive. The child's platelet count at birth was 13,000 per cu. mm. and he "bled easily and prolonged from small punctures." His platelet counts remained depressed for a two-months' period after which time he was not seen for two years. When

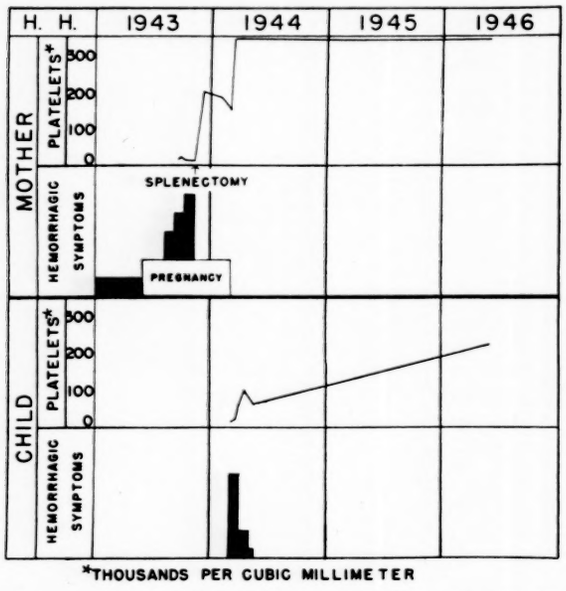

FIG. 4. Case IV. Clinical course and blood platelet counts of mother and child.

examined at this time he was entirely asymptomatic and his platelet count was 223,000 per cu. mm.

CASE V. Mrs. G. S. was a twenty-nine year old white registered nurse. At the age of twenty-two she first noticed the onset of purpura in the form of ecchymoses, particularly on the legs. Her menses became prolonged to twelve or fourteen days and the flow profuse. On one occasion she passed a small amount of bright red blood rectally. The patient was hospitalized in another city and the diagnosis of purpura hemorrhagica established. Fluid aspirated from the sternum was reported to her as normal. She was treated symptomatically for two years without significant improvement. The past, family and social histories were not remarkable. When first seen at this clinic at the age of twenty-four, physical examination revealed no abnormalities aside from several petechiae about each ankle and a few small ecchymoses on the legs. Laboratory data were: repeated blood platelet counts below 100,000 and frequently in the range of 30,000 to 40,000 per cu. mm. Clot retraction was poor and the tourniquet test was positive. Splenectomy was performed without untoward event and the postoperative course was uncomplicated. The pathologist's report was: "Gross examination: the specimen consists of a spleen weighing 161 grams and measuring 11 × 7.5 × 3.5 cm. It is firm and spongy in character, red-brown in color. It does not appear grossly abnormal. Microscopic examination: Malpighian corpuscles somewhat hyperplastic. Sinusoids relatively empty. Diagnosis: Consistent with thrombocytopenic purpura." On the twelfth postoperative day the platelet count rose to 590,000 per cu. mm. No further purpuric manifestations have been observed. At the age of twenty-six the patient became pregnant. The gestation was uneventful and at term a female child was delivered at another hospital. The infant apparently had no hemorrhagic stigmata at birth. Unfortunately platelet counts could not be performed, but examinations of blood films during the first week after birth revealed a marked diminution in their number. On blood films prepared six and twelve months later platelets were present in normal numbers.

SUMMARY

A review has been made of the literature of pregnancies complicated by purpura hemorrhagica. Reports of thirty-nine such pregnancies have been found and seven similar ones are described. In the total group of forty-six pregnancies the over-all maternal mortality was 8.7 per cent, while that of the child was 26.1 per cent. One-half of the children born living had congenital thrombocytopenic purpura. Within a few months their platelet counts increased to normal and almost invariably remained elevated. No correlation was found between the age, parity, manner of feeding the infant, presence or absence of the spleen in the mother and the syndrome in the child. The theories of the pathologic physiology of purpura hemorrhagica were briefly reviewed and it was suggested that congenital thrombocytopenic purpura might be the result of the transfer of an immune body, hormone or other substance across the placental membrane which depresses platelet formation in the infant. The presence of this substance was quite inde-

pendent of the presence or absence of the spleen in the mother.

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Intestinal Lavage in the Potassium Intoxication of Lower Nephron Nephrosis*

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ACUTE temporary renal insufficiency as characterized by lower nephron nephrosis has recently become more frequently recognized. It has been learned that through intelligent restriction of fluids and supplying adequate glucose many patients with anuria due to this disorder can carry on until renal function resumes.[1,2] Of the remainder of subjects with this syndrome who are not drowned due to overenthusiastic therapy, many die a cardiac death. The probable cause of this in some instances is an elevation of the serum potassium to critical levels.

Much effort has been devoted to devising a method for clearing the blood of products of metabolism usually excreted by the kidney.[3] In this study lavage of the upper small intestines[4,5,19,20] and stomach has been utilized because in our hands this has been a simple and effective means of extrarenal clearance of potassium and urea. This paper reports our experience with this method in one long-term study in a case of lower nephron nephrosis. Lavage was instituted in this case to lower a critically high serum potassium and to correct a grossly abnormal electrolyte pattern. In two acute clinical studies, one with malignant hypertension and one with chronic glomerulonephritis, lavage was performed to test the method.

METHODS AND MATERIALS

In this study a Miller-Abbott double lumen tube was inserted through the nose and passed from 2 to 5 feet beyond the pylorus. After this a Levine gastric suction tube was passed through the other nostril until the tip entered the stomach. The solution used for lavage of the mucosa in this study was a modification of that already suggested.[11] It contained sodium chloride, sodium bicarbonate, calcium chloride and magnesium chloride in concentrations similar to plasma, and glucose in concentration sufficient to supply the caloric requirement of the body as well as possible. (Table 1.) The disparity between the proposed solution and the concentrations of the electrolytes in the fluid utilized is due to the unrefined way in which the solution was prepared.

TABLE 1
MODIFIED "P" SOLUTION

Compound	Gm./L.
Sodium chloride	6.0
Sodium bicarbonate	3.0
Calcium chloride	0.1
Magnesium chloride	0.1
Glucose	20.0

This solution was introduced through the Levine tube at a rate as near 10 L. per twenty-four hours as possible. Wangensteen-type suction was applied to the evacuation lumen of the Miller-Abbott tube and constant negative pressure maintained. The solution was analyzed before and after passage through the tubing and bowel with determinations of urea, sodium, potassium, chloride and fluid volume. On occasions samples were obtained at five- to six-hour intervals and analyzed. The serum sodium was determined gravimetrically,[14] and the urea, CO_2 combining power and chlorides (plasma) by the conventional methods.[15–17] The serum potassium and the sodium and potassium in other fluids were measured by means of the Perkin-Elmer flame photometer.

In three subjects such a procedure was carried

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out. One, a colored female, was in the terminal stages of glomerulonephritis with uremia, anasarca and oliguria. The Miller-Abbott tube was passed under fluoroscopic control 2 feet beyond the pylorus. Lavage of the intestine was carried out for six hours. The second, a white male, was

TABLE II
COMPOSITION OF SOLUTION BEFORE AND AFTER LAVAGE IN FIRST PATIENT

Substance	Conc. before Lavage	Conc. after Lavage
Na (mEq./L.)	109	96
K (mEq./L.)	0	3.8
Cl (mEq./L.)	92	91
Urea (mg.%)	0	156

afflicted with malignant hypertension, moderate uremia and slight cardiac decompensation. Lavage of the bowel in this case was carried out for twenty-one and one-half hours with the double-lumen tube 2 feet beyond the pylorus. The third, a colored male, had acute renal insufficiency to be described in detail in this communication.

RESULTS

The subject with glomerulonephritis was not studied over a long enough period to make blood changes likely; therefore, samples of fluid which passed through this system were analyzed only for content of sodium, potassium, chloride and urea. Initial blood analyses revealed the blood urea to be 274 mg. per cent, CO_2 combining power 12.5 mEq./L., chloride 92 mEq./L., serum sodium 139 mEq./L., serum potassium 5.5 mEq./L. (Table II.) Urea and potassium concentrations in the perfused fluid were about one-half to two-thirds that of the concentrations of these constituents in the blood serum without appreciable change in the other constituents of the "P" solution used in perfusion.

Lavage was instituted in the patient with malignant hypertension for twenty hours with "P" solution and one and one-half hours with distilled water. The distal tube was 2 feet beyond the pylorus. Blood levels before and after, and changes in fluid composition before and after lavage, are tabulated in Table III. The urea reached a concentration one-half that of the blood urea and potassium was equal to that of the serum potassium. Six and two-tenths gm. of urea and 1.25 gm. of potassium were removed in twenty-four hours of lavage.

TABLE III
COMPOSITION OF FLUID AND BLOOD BEFORE AND AFTER LAVAGE IN PATIENT TWO

Substance	Conc. before Lavage	Conc. after Lavage	Conc. in Blood before Lavage	Conc. in Blood after 20 Hr.
Na (mEq./L.)	109	109	130	130
K (mEq./L.)	0	3.1	3	2.8
Cl (mEq./L.)	92	88	99	81
Urea (mg.%)	0	60	120	80
CO_2 (mEq./L.)	...	.....	23	29

CASE REPORT

A forty-three year old colored male was well until a frontal headache persistent for eighteen hours led him to visit the clinic. At that time the urine was normal. Within the next twelve hours he had several generalized convulsions necessitating hospital admission.

Upon admission he was unconscious. He appeared well nourished and of average size with normal blood pressure, pulse, respiration and temperature. He was responsive only to painful stimuli and all reflexes were absent. The remainder of the physical examination was normal. The next day his temperature reached 104°F. and nuchal rigidity ensued. Sodium sulfadiazine, 5 gm. in 500 cc. M/6 lactate solution, and penicillin were given intravenously.

Following this it was noticed that the urine volume was limited. The sulfadiazine was discontinued and streptomycin substituted. An indwelling catheter was inserted and urine volume remained below 50 cc. per day for five days. Fluid was limited to 750 cc. of 20 per cent glucose intravenously per day plus a volume equal to the previous day's urinary output. He developed a small amount of edema but urine flow increased to 300 cc. per day on the sixth day. This urine was of 1.010 specific gravity and contained 36 mg. per 100 cc. of urea and 1.5 gm. of sodium chloride in the day's urinary output. Urine volume and composition remained about this level for the next ten days. The blood urea

had climbed steadily to a level of 291 mg. per cent at this time and the CO_2 combining power had decreased to 10 mEq./L. in spite of administration of a portion of the prescribed day's fluid in the form of one-sixth molar sodium lactate on several occasions. The patient was

TABLE IV
COMPOSITION OF DISTILLED WATER BEFORE AND AFTER LAVAGE IN PATIENT THREE

Substance	Conc. before Lavage	Conc. after Lavage	Conc. in the Blood
Na (mEq./L.)	0	83	148
K (mEq./L.)	0	3.8	4.8
Cl (mEq./L.)	0	95	96
Urea (mg.%)	0	186	212

stuporous and there was a "urea frost" on his brow. Heart rate was 50 and electrocardiogram showed changes characteristic of moderately severe hyperpotassemia.[18] There was auricular standstill with idioventricular rhythm. The QRS was 0.12 of a second in duration and the T waves were tall and spiked. Tubes were passed for intestinal lavage, the Miller-Abbott tube being fed 5 feet beyond the pylorus. The first two days a solution of 0.9 per cent saline and 2 per cent glucose was used, then the modified "P" solution was utilized for lavage. Five to eight L. of fluid per day were passed through the system. After twenty-four hours of lavage an electrocardiogram showed the heart rate and rhythm to be normal with a QRS duration of 0.06 of a second and normal T waves. Later the CO_2 and chloride became normal. The blood urea fell to 212 mg. per cent. Because the serum potassium had fallen from 7.2 to 4.8 mEq./L., lavage was discontinued on the fourth day of lavage and the nineteenth day of illness. No significant increase in edema occurred during the period of intestinal lavage. Blood chemistry values varied only slightly following this until the twenty-second day of illness when diuresis ensued. Even then the urine remained dilute but the blood urea fell slowly and steadily. He became afebrile and asymptomatic and was discharged on the thirty-fourth hospital day. (Fig. 1.)

This patient was slightly edematous and the small amount of sodium lactate he could tolerate did not alter his CO_2 combining power. After one day of lavage with "P" solution the

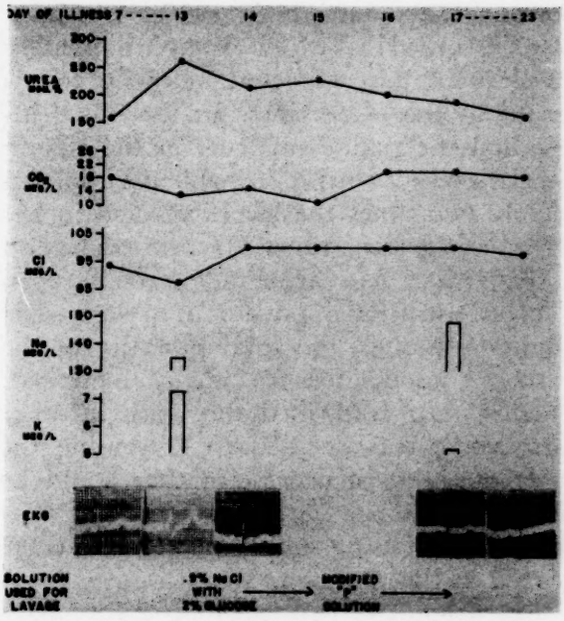

FIG. 1. Subject in whom lavage of intestine was used from the thirteenth through the seventeenth days of illness.

CO_2 combining power increased from 10 mEq./L. to 22 mEq./L. Potassium was removed in the fluid in a concentration about two-thirds to three-fourths that of the patient's serum level. The urea concentration of withdrawn solution was equal to blood urea concentration (291 mg. per cent). For a six-hour period distilled water was used for lavage and its composition before and after are tabulated. (Table IV.)

After two months random urine concentration was 1.020 and phenolsulfonthalein excretion was 30 per cent in fifteen minutes, 70 per cent in one hour and the blood urea was 20 mg. per cent. Blood pressure remained normal during the entire hospital stay and after discharge.

It is known that the gastric juice contains a concentration of potassium reported to be two to five times the concentration of that found in the serum of the individual at the same time. To confirm this a Levine tube was inserted into the stomach of two individuals and continuous suction by Wangensteen apparatus was maintained for two hours on each of the individuals. At the end of two hours histamine was given to the patient and continuous suction again instituted for a total of one hour. These samples were analyzed and it was found that in one subject, who was completely

normal, the potassium in the gastric juice was 16 mEq./L. which is approximately three times that expected in the patient's serum at the same time. In the other individual the potassium level in the gastric contents was 9.5 mEq./L. which is approximately two times the level expected in her serum at the same time. The administration of histamine had absolutely no effect on the concentration of potassium in the gastric contents, though the total quantity of the gastric contents was decidedly increased. Having thus confirmed the work of other authors, it was decided to determine the total quantity of potassium that could be cleared from an individual's stomach by rapid lavage using simply two Levine tubes placed in the stomach.

Consequently two normal individuals, one a white male and one a white female, were subjected to this procedure. In the first individual 3,000 cc. of fluid were introduced into one of the Levine tubes and an exactly similar quantity withdrawn from the other in a period of three hours. The composition of the original fluid was 5 per cent glucose in normal saline solution. After the solution had been passed through the system the concentration of urea was 20 mg./100 cc. and that of potassium 1.2 mEq./L. This indicated the removal of 0.6 mg. of urea in the three-hour period. A total of 150 mg. of potassium was removed during this same time.

In the second individual 2,500 cc. of fluid were passed through the system in a three-hour period. The urea concentration in the fluid after lavage was 24 mg./100 cc. and that of potassium 4 mEq./L. A total quantity of 0.6 gm. of urea per three hours was removed in the second individual and a total quantity of 185 mg. of potassium was removed in the three-hour period.

Before this investigation was completed an individual with clinical and chemical evidence of potassium intoxication was seen by one of the authors (A. J. C.) and two tubes inserted into the stomach and lavage maintained with the aforementioned "P" solution, a total of about 16 L. of fluid being passed through the system each twenty-four hours. There was no improvement in the patient's clinical status and, actually, there was very little potassium removed during the procedure. This was confirmed by electrocardiographic and chemical studies. The reason for this is not obvious but death ensued in this patient in spite of lavage of the stomach.

COMMENTS

Lavage of the stomach and small bowel by the method described is quite simple. In all cases in which it was used the mechanism was functioning within three hours after attempts were begun. The difficulty of passing a Miller-Abbott tube long distances down the small bowel has been pointed out elsewhere but it has been shown here that passage 2 to 5 feet beyond the pylorus is adequate and usually simple. Two complications were encountered but surmounted. One patient developed pneumonitis and this emphasized the necessity of administering prophylactic antibiotics. In all cases some absorption of the lavage fluid was encountered but this can be kept to a minimum by careful supervision. The volume of fluid absorbed should obviously be subtracted from the proposed fluid intake.

In the subject treated for four days the total fluid used in lavage was 28 L. Of this amount 26.5 L. were recovered.

Lavage of the small intestine was chosen because it avoids many of the difficulties posed by other methods of clearance of products of metabolism. Peritoneal lavage[6–8] necessitates surgery and asepsis, and mechanical difficulties as well as fluid and electrolyte absorption are usually encountered. External dialysis[9,10] is cumbersome and demands heparinization of the patient, which is not accomplished without danger and spending of much time. Colonic lavage[11] is associated with fluid and electrolyte absorption. Exsanguino-transfusion[3] seems an inefficient way of ridding the body of excess potassium.

Urea was effectively removed, as much

as 49.5 gm. in twenty-four hours. When the patient is under basal conditions with adequate glucose to furnish caloric needs, removal of 1 to 3 gm. of urea every twenty-four hours will afford a balance.[4]

We consider more important than this the fact that the third subject had hyperpotassemia that had progressed until it produced auricular standstill with idioventricular rhythm and a rate of 50 and QRS complex of 0.12 of a second duration in Lead I of the electrocardiogram. The serum potassium appeared to be approaching a fatal level. After twenty-four hours of intestinal lavage the heart had reverted to normal rhythm, and the rate had increased to 68 per minute. Potassium can be removed by lavage of the upper 2 feet of small bowel, a concentration three-fourths of that of the blood obtained in the lavaged fluid. As much as 4.1 gm. of potassium could be removed in twenty-four hours of lavage. This is pointed out for three reasons: (1) to emphasize the necessity in acute renal shutdown of regular electrocardiograms and serum potassium determinations to decide when lavage of the intestine is necessary; (2) to confirm the observation that hyperpotassemia is a real threat in management of the individuals with acute renal insufficiency and (3) that intestinal lavage is a satisfactory mode of overcoming this definite hazard.

Investigators in the past have concentrated their efforts and attention on removal of accumulated urea from the blood stream.[4,7,8] It has been shown repeatedly that simple elevation of the blood urea by ingestion of urea causes practically no clinical toxicity.[12,13] This absence of toxicity of urea does not gainsay the value of urea, non-protein nitrogen and similar chemical determinations in the blood as a reasonably good index of the degree of retention of other more toxic substances. The hazard posed by the hyperkalemia occurring with acute renal insufficiency, however, appears to assume increasing importance and probably accounts for most of the cardiac deaths during anuria in "undrowned" patients.

The total quantity of potassium and urea removed by intestinal lavage in four patients is shown in Table v. The results have been arranged to indicate the volume of lavage fluid used to remove urea in terms of urea nitrogen and potassium during the same run. This table allows some basis for comparison with clearance of the same substances by the artificial kidney.

TABLE V

TOTAL QUANTITY OF POTASSIUM AND UREA REMOVED BY INTESTINAL LAVAGE IN FOUR INDIVIDUALS

Subject	Lavage Fluid (per 24 hr.-cc.)	Urea N Removed (per 24 hr.-gms.)	K Removed (per 24 hr.-mEq.)
A	6,000	7.9	32.5
B	12,000	3.3	36.0
C	24,000	23.2	102.5
D	24,000	11.9	90.0

SUMMARY

1. A simple but effective method of lavage of the stomach and upper intestine is discussed.

2. The occurrence and therapy of hyperkalemia in a patient with acute renal insufficiency has been described.

3. The successful removal of potassium and urea by upper intestinal lavage is demonstrated in three individuals. The third subject had lower nephron nephrosis with potassium poisoning which disappeared following intestinal lavage.

4. It is likely that other forms of acute temporary renal insufficiency may respond favorably to a similar mode of management.

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Review

Peritoneal Lavage as an Effective Means of Extrarenal Excretion*

A Clinical Appraisal

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LAVAGE of the peritoneal cavity as a means of substituting for the kidneys in cases of renal insufficiency first was attempted clinically in 1923. In the past twenty-five years,† in so far as we have been able to determine, 101 cases of renal insufficiency in which peritoneal lavage has been employed have been reported in the literature (Table 1), although undoubtedly the procedure has been attempted, either successfully or unsuccessfully, in numerous unreported instances. Clinical experience with this procedure has diverged widely and many questions, the answers to which are still wanting, have been raised. It seems appropriate, therefore, to attempt to analyze the data at hand in the hope of answering some of the questions.

BASIC PRINCIPLES OF DIALYSIS

Attempts to substitute for the failing kidney may be based, in general, on the following five principles: (1) Crystalloids in solution will diffuse across semipermeable membranes in a manner which tends to equalize the concentration of each substance on both sides of the membrane. (2) Colloids such as protein molecules ordinarily will not diffuse across a semipermeable membrane. (3) In the normal kidney, water and crystalloids filter across the wall of the glomerular capillaries to produce a glomerular filtrate similar to blood plasma except for the absence of protein. (4) Since the action of glomerular filtration is considered essentially a physical action, it should be possible to substitute a semipermeable membrane for the glomerular filtering surface. (5) Large quantities of water and certain crystalloids needed by the body are selectively reabsorbed by the renal tubules. Although there can be no substitute for the selective resorptive function of the tubules, necessary water and crystalloids which the tubules ordinarily would conserve can be replaced by parenteral routes.

EXPERIMENTAL STUDIES OF PERITONEAL LAVAGE

The peritoneum long has been recognized as an excellent dialyzing membrane with a filtering surface of approximately 22,000 sq. cm. in the average adult.[46] Since an understanding of the fundamental physiologic principles on which peritoneal lavage is based is necessary if all precautions are to be taken to avoid complications, knowledge of some of the early observations on the physiologic behavior of the peritoneum was reviewed in a previous communication.[37] Especially worthy of emphasis are the studies of Darrow and Yannet,[15] who found that introduction into the peritoneal cavity of a solution poor in salt resulted in loss of electrolytes from the blood, notably

† The past twenty-five years means 1923 through 1948. Data for 1949 were not available at the time this paper was written.

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sodium and chloride, shift of extracellular water into cells and signs and symptoms of clinical dehydration; whereas injection of a hypertonic solution of sodium chloride produced shift of water from cells into the extracellular compartment, hyperchloremia,

TABLE I
CASES IN THE LITERATURE IN WHICH PERITONEAL LAVAGE HAS BEEN REPORTED TO HAVE BEEN USED: 1923–1948 INCLUSIVE

Year	Author	Total Patients	Patients Recovered	Patients Died
1923	Ganter[23]	1	0	1
1927	Heusser and Werder[26]	3	0	3
1934	Balázs and Rosenak[4]	2	0	2
1938	Wear, Sisk and Trinkle[52]	5	1	4
1938	Rhoads[42]	2	0	2
1946	Fine, Frank and Seligman[18]	4	1	3
1946	Weiss and Mills[53]	1	0	1
1946	McGraw[33]	1*	..	..
1946	Reid, Penfold and Jones[41]	1	1	0
1947	Smith and Eaves[48]	4	3	1
	Goodyear and Beard[24]	1	1	0
	Muirhead and co-workers[35]	3	1	2
	Pearson[38]	1	0	1
	Robertson and Rutherford[43]	1	0	1
	Buckley and Scholten[11]	1	0	1
	Strean, Korenberg and Portnuff[50]	1	1	0
	Grossman, Ory and Willoughby[25]	1	1	0
	Doenges and Strahan[16]	1	0	1
	Connolly and Lempka[13]	3	3	0
	Bassett and co-workers[5]	1	0	1
1948	Kop[29]	21	10	11
	Bloxsom and Powell[10]	1	1	0
	Sterling[49]	4	0	4
	Bergqvist[7]	1	0	1
	Fretheim and Selvaag[21]	3	1	2
	Allbee and Mayfield[2]	1	1	0
	Cave[12]	2	0	2
	Odel, Ferris and Power[37]	3	2	1
	Reid[40]	5	2	3
	Localio, Chassin and Hinton[30]	1	1	0
	Batson and Peterson[6]	1	1	0
	McGinn, Miale and Frye[32]	1	0	1
	Frank and co-workers[20]	14	3	11
	Toth and King[51]	1	1	0
	Ask-Upmark and Hogeman[3]	1	0	1
	Longley[31]	1	0	1
	Pendino and Hampton[39]	1	1	0
	Moody[34]	1	0	1
	Total	101	37	63

* Outcome unknown.

hypernatremia, hydremia and tissue edema. These observations and others[47] have served to illustrate that, regardless of whether a natural or an artificial membrane is used for dialysis, the composition of the fluid with which it is bathed is of the utmost importance, and that the success or failure of any artificial means of excretion will depend largely on the use of a suitable perfusing fluid.

Many investigators who have used the peritoneum as a dialyzing membrane have failed both experimentally and clinically in the treatment of uremia, largely because water and electrolyte balance were not sufficiently considered. Recently, Abbott and Shea[1] have carried out extensive investigations of nephrectomized animals. Their studies have substantiated data previously reported that the use of solutes not containing sodium chloride resulted in severe depletion of plasma chloride, evidence of dehydration, hemoconcentration and shock, whereas use of fluids in which the concentration of chlorides was greater than that of normal blood plasma resulted in increase of plasma chlorides, depletion of plasma carbon dioxide combining power, evidence of hemodilution and edema.

CLINICAL OBSERVATIONS OF PERITONEAL LAVAGE

Acute renal failure and uremia occur frequently in cases in which irreversible renal changes cannot be demonstrated. Although the pathogenesis is not clear, acute degenerative changes have been shown to develop within a very short time after the initial injury. Also it has been shown that cellular regeneration likewise begins within a few days. In considering, then, the problem of peritoneal lavage, it is extremely important to bear in mind the concepts that, in the absence of chronic organic renal damage, acute failure is a self-limiting disease and that the reparative power of the kidney is great.

In the past the mortality rate associated with this condition, unfortunately, has been high because the patient has been unable to withstand the effects of rapidly progressing acute uremia for a period sufficient to allow histologic and functional renal regeneration to take place. The procedure of peritoneal lavage, as is true of other means of extrarenal excretion, actually has little or no direct effect on hastening the reparative process in the kidney. Its function is that of supplying an avenue of elimination for toxic end products of metabolism during

the period of suppressed renal function, thereby delaying progression of renal insufficiency and the development of resulting uremic symptoms.

Types of Lesions in Association with Which Peritoneal Lavage Has Been Employed. Peritoneal lavage, therefore, as a therapeutic measure should be considered in those situations associated with acute urinary suppression and temporary renal damage (reversible lesions). Transfusion with incompatible blood, intoxication from sulfonamides, severe burns, poisoning with heavy metals or other drugs, toxemia of pregnancy, the "crush injury syndrome," hemolytic reactions, shock, certain urologic and surgical procedures, all may produce acute renal failure and uremia, which should be amenable to artificial removal of waste products, with ultimate recovery of the patient. Acute glomerulonephritis and acute pyelonephritis with anuria may in some instances be included in this category. Recently it has been shown[8] that methyl alcohol diffuses readily across the peritoneum, and peritoneal lavage therefore has been suggested as a method for treatment of acute intoxication from methyl alcohol. Of the 101 reported cases in sixty-three the lesions were reversible (Table II) and the patients in thirty-two of the sixty-three cases have recovered (51 per cent). (Table III.)

TABLE II

DIAGNOSES AND RESULTS IN CASES WHICH HAVE BEEN REPORTED IN THE LITERATURE

Type of Lesion	Total Patients	Patients Recovered	Patients Died
Reversible:			
Transfusion with incompatible blood	14	9	5
Sulfonamide intoxication	10	5	5
Mercuric chloride poisoning	12	7	5
Postoperative anuria	6	2	4
Toxemia of pregnancy	5	5	0
Postoperative hemolytic reactions	3	0	3
Benign hypertrophy of prostate with obstruction	3	1	2
Poisoning with carbon tetrachloride	2	0	2
Poisoning with alcohol	2	1	1
Obstructive hydronephrosis	2	1	1
Acute glomerulonephritis	2	0	2
Renal and vesical calculi	1	1	0
Bleeding duodenal ulcer	1	0	1
	63	32	31
Irreversible:			
Glomerulonephritis—subacute or chronic	16	0	15*
Hypertensive cardiorenal disease	8	0	8
Prostatic carcinoma with obstruction	3	0	3
Vesical carcinoma with obstruction	2	0	2
Cervical carcinoma with obstruction	1	0	1
Renal amyloidosis	1	1	0
Lipoid nephrosis	1	1	0
	32	2	29
Diagnosis indeterminate	6	2	4

* One case chronic nephritis—outcome unknown.

TABLE III

SUMMARY OF CASES REPORTED IN THE LITERATURE

Category	Total Patients	Patients Died	Recovered	
			No. of Patients	Per cent
Total	101	63	37	37
Reversible lesions	63	31	32	51
Irreversible lesions	32*	29	2	6
Diagnosis indeterminate	6	4	2	33

* Outcome in one case unknown.

From the standpoint of therapeutic value, patients who have renal failure and uremia secondary to advanced organic renal parenchymal damage (irreversible lesion) should be considered as unsatisfactory candidates for peritoneal lavage because, although temporary alleviation of symptoms and regression of laboratory evidence of azotemia may occur during the period of lavage, signs and symptoms of progressive renal failure and uremia again ensue as soon as the procedure has been terminated. The intrinsic risks and hazards attending the procedure are sufficiently great to make its justification for use in such cases debatable. In thirty-two cases the lesion responsible for renal insufficiency was judged to be irreversible (Table II); twenty-nine of the patients died and only two (6 per cent) were known to have recovered. (Table III.) The diagnoses in the latter two cases would indicate long-term renal disease associated either with no retention of nitrogen or with slowly progressive renal insufficiency. The fate of one patient in this group was not stated although, considering that the diag-

nosis was chronic glomerulonephritis, an ultimately fatal outcome may be assumed. In six cases the diagnosis was unknown although the outcome in four of these was reported as unsuccessful.

TABLE IV
DECREASE IN CONCENTRATION OF NITROGEN IN BLOOD DURING PERIOD OF PERITONEAL LAVAGE

Type of Lavage	Cases	Urea		Non-protein Nitrogen		Data Unreported, Cases
		Cases	Average Decrease, mg./100 cc.	Cases	Average Decrease, mg./100 cc.	
Intermittent*	22	8	116	8	40	6
Continuous†	75	35	117	33	56	7
Unknown	4					

* Number of lavages, 1 to 6; duration of periods of lavage, 15 minutes to 6 hours.
† Duration of lavage, 1 to 21 days: average days per case, 6.

Excretion of Nitrogen. Perusal of the literature should leave no doubt in the mind of the reader that peritoneal lavage is an effective means of removing stored metabolic waste products from the blood and tissues of uremic patients. In almost all instances in which the procedure has been employed, marked decrease in concentration of blood urea or of non-protein nitrogen has been noted, with recovery of large amounts of nitrogen in the perfusate. Of ninety-seven cases in which concentration in the blood, either of urea or of non-protein nitrogen, was reported before and after lavage, in seventy-five lavage was continuous and in twenty-two repeated intermittent lavage of varying duration was employed. (Table IV.) It is of interest that the average decrease in concentration of non-protein nitrogen or of urea in the blood was essentially the same regardless of the type of lavage used.

Continuous Versus Intermittent Lavage. Although the foregoing values tend to indicate that continuous lavage and repeated periods of intermittent lavage of short duration are equally effective, in so far as elimination of nitrogen is concerned, the relative merits of one method over the other have at times been questioned. Abbott and Shea,[1] after extensive investigations on nephrectomized animals, have concluded that intermittent injection and withdrawal of a solution having a chemical composition similar to that of interstitial fluid, and made hypertonic by addition of dextrose, is the most effective method of lavage. More recently, Frank and his colleagues[20] have emphasized the value of intermittent lavage in reducing the incidence of peritonitis during the period of lavage.

TABLE V
RESULTS IN RELATION TO NATURE OF LESION AND TYPE OF LAVAGE

Method of Lavage and Type of Lesion	Total Patients	Recovered		Died	
		No. of Patients	Per cent	No. of Patients	Per cent
Continuous:					
Reversible	52	29	56	23	44
Irreversible	21	2	10	19	90
	73*	31	42	42	58
Intermittent:					
Reversible	11	5	45	6	55
Irreversible	11	0	0	11	100
	22	5	23	17	77
Indeterminate	6	..	..	..	..

* In two cases in which treatment was by the continuous method, the outcome was not reported; hence, both cases were included in the indeterminate group.

Of seventy-three cases in which lavage was continuous, thirty-one (42 per cent) patients recovered, whereas of twenty-two cases in which lavage was intermittent, five (23 per cent) patients recovered. (Table V.) This disparity in the number of cases in the two groups precludes the drawing of accurate conclusions from these data, but the difference in recovery rate suggests that, in general, continuous lavage may be the more effective method. Future experience, both investigative and clinical, will be necessary in order to elucidate the various factors on which the relative effectiveness of the two methods of procedure are contingent.

Causes of Death. Of forty cases in which the cause of death was reported, three complications accounted for death in 88 per cent of the cases. (Table VI.) In thirteen cases (33 per cent) death was ascribed to uremia. In these cases the lavage procedure failed and signs and symptoms of progressive renal insufficiency supervened. In sixteen cases (40 per cent) death was due to pulmonary edema. It can be assumed that this complication was brought about by use of an unbalanced perfusing fluid or by injudicious and excessive use of parenteral fluids, although hypoproteinemia or acute myocardial failure could have been a factor. Peritonitis was given as a primary cause of death in six cases (15 per cent), although bacterial contamination of the peritoneal fluid was commented on in several additional cases. Since in twenty-two cases (16 + 6; 55 per cent) death could be ascribed directly to the procedure, it seems indicated at this time to consider further the procedure itself in an attempt to discover errors in technic.

TABLE VI
CAUSES OF DEATH

Cause	No. of Cases	Per cent
Uremia	13	33
Pulmonary edema	16	40
Peritonitis	6	15
Pulmonary embolism	2	5
Salt depletion	1	2.5
Septicemia	1	2.5
Exhaustion and shock	1	2.5
	40	
Cause not stated	23	

Incidence of Peritoneal Infection. Infecting organisms may enter the peritoneal cavity with the dialyzing fluid in and around the peritoneal tubes, or in retrograde fashion from the non-sterile suction system. It has also been suggested[20] that if the intestinal wall of uremic patients is more permeable to bacteria than that of normal persons, infecting organisms may migrate across the wall of the intestine from the lumen into the peritoneal cavity.

Of sixty-two cases in which the presence or absence of peritoneal infection was reported, eight patients were treated by intermittent lavage. Of the eight cases, bacterial contamination of the peritoneal cavity was reported in three. (Table VII.) Of fifty-four cases in which treatment was by continuous lavage, peritoneal infection was reported in twenty-six (48 per cent). Kolff[27] has expressed the opinion that to employ peritoneal lavage for longer than thirty-six hours is to increase greatly the hazard of peritonitis. Recently, Frank and his colleagues[20] have expressed a similar opinion and, for this reason, they have abandoned continuous lavage in favor of repeated intermittent lavage through a single two-way peritoneal tube.

TABLE VII
INCIDENCE OF PERITONEAL INFECTION

Type of Lavage	Total Cases	Cases of Infection	
		Yes	No
Intermittent	8	3	5
Continuous—days			
1	2	0	2
2	7	2	5
3	5	3	2
4	7	2	5
5	7	1	6
6	8	8	0
7	4	3	1
8	3	3	0
9	1	0	1
10	4	1	3
12	2	2	0
15	1	0	1
16	1	0	1
17	1	1	0
21	1	0	1
	54	26	28

The incidence of peritoneal infection in the cases reported appears to indicate but little advantage of intermittent over con-

tinuous lavage, although the disparity in numbers of cases in the two groups admittedly is large. It is doubtful that any significant conclusions can be drawn from the data on the incidence of peritoneal infection in relation to duration of continuous lavage. Of the twenty-six cases in which infection was reported to have occurred, the period of lavage varied in twenty-five from two to twelve days. However, in three cases in which continuous lavage was carried out for longer periods (fifteen, sixteen and twenty-one days, respectively), evidence of peritoneal infection was absent. We have encountered peritoneal infection in all of our cases but in none did it become a significant clinical complication. We are of the opinion, therefore, that if peritoneal infection can be prevented, or if it can be kept under control by careful preparation of fluid, by aseptic care of the operative sites and by adding antibiotics to the perfusing fluid and administering them parenterally, continuous lavage should be employed until adequate renal function is resumed.

TABLE VIII

ACID-BASE BALANCE: CASES REPORTED IN THE LITERATURE

Solution	Total Cases	Hyperchloremia			Acidosis			Presence or Absence of Edema		
		Chlorides Reported	Yes	No	CO_2 Reported	Yes	No	Edema Reported	Yes	No
0.8% NaCl	5	0	..	..	0	..	..	0	..	..
0.9% NaCl	4	2	1	1	2	2	0	2	2	0
4.2% Dextrose	1	0	..	..	0	..	..	0	..	..
5% Dextrose	1	1	0	1	0	..	..	1	1	0
Ringer's	9	5	1	4	4	3	1	6	4	2
1.8% NaCl	5	1	1	0	0	..	..	1	1	0
Rhoads'	2	1	1	0	1	1	0	2	0	2
Hartmann's	6	2	0	2	3	1	2	4	3	1
Mod. Tyrode's I	30	18	9	9	21	19	2	25	23	2
Mod. Tyrode's II	7	4	1	3	5	5	0	4	4	0
"A"	4	3	0	3	3	1	2	4	2	2
Kolff's	21	21	6	15	19	0	19	0	..	..
"P"	3	3	0	3	3	0	3	3	0	3
Modified "P"	1	1	0	1	1	0	1	1	1	0
Unknown	2	..	..	..	..	..	..	1	1	0
	101	62	20	42	62	32	30	54	42	12

Solutions Used. Various solutions have been used for peritoneal lavage, some of which, although generally considered to be physiologic solutions, appear to be unsatisfactory for peritoneal lavage in the light of previous experimental work on the interchange of fluid and crystalloids across the peritoneum. Balázs and Rosenak[4] used 0.8 per cent solution of sodium chloride in one case and 4.2 per cent solution of glucose in another. Ganter[23] used 0.8 per cent solution of sodium chloride in his case, but information is not available as to the behavior of plasma chlorides and carbon dioxide combining power of the blood or as to the presence or absence of edema in these three cases. The various solutions which have been employed and the frequency of their use are recorded in Tables VIII and IX. Table VIII is somewhat incomplete owing to the fact that the presence or absence of hyperchloremia, acidosis or edema, either pulmonary or peripheral, was not mentioned in all reports. It appears to be significant, however, that in twenty (32 per cent) of sixty-two cases in which values for

chloride in plasma were reported, concentrations of chloride greater than normal (103 mEq./L.) developed at some time during the period of lavage. Of sixty-two cases in which values for carbon dioxide combining power of the plasma were given, the authors reported decrease in carbon dioxide combining power of the plasma during the period of lavage, to less than normal (27 mEq. of HCO_3^-/L.) in thirty-two (52 per cent). In forty-two (78 per cent) of fifty-four cases in which the presence or absence of edema was noted, clinical edema, either pulmonary or peripheral, developed during the period of lavage. Since these three phenomena are expressions of disturbances in electrolyte balance, further examination of the solutions used and of their constituent parts seems indicated.

Chloride Balance. In Table VIII it is evident that seven solutions were used in the twenty cases in which hyperchloremia developed. These solutions were 0.9 per cent solution of sodium chloride, 1.8 per cent solution of sodium chloride, Ringer's solution, Rhoads' solution, modified Tyrode's solutions I and II as modified by Frank and his colleagues,[20] and Kolff's solution.[28] Tables IX and X give the composition of these various solutions. It will be noticed (Table IX) that in the above named solutions with one exception (Kolff's solution) the chloride content is excessively high as compared with that of blood plasma. When any of these solutions are perfused through the peritoneal cavity, therefore, diffusion of excessive amounts of chloride and sodium across the peritoneal membrane would be

TABLE IX
ELECTROLYTE COMPOSITION OF SOLUTIONS USED FOR PERITONEAL LAVAGE

Ions mEq./L.	Solution*												
	Normal Plasma	0.9% NaCl	1.8% NaCl	Ringer's	Locke's	Rhoads'	Hartmann's	Tyrode's I	Tyrode's II	"A"	Kolff's	"P"	Modified "P"
Na^+	142	154	308	157	156	276	130	151	134	131	127	139	143
K^+	5			4	3	5	4	3	3	5	5	3	3
Ca^{++}	5			5	8	4	4	2	4	4		2	2
Mg^{++}	3							2	5	1		2	2
HCO_3^-	27			3	2			12	12	26	24	36	24
Cl^-	103	154	308	163	165	257	110	145	134	114	108	109	109
HPO_4^{--}	2							1		1		1	1
SO_4^{--}	1												
Org. acids	6												
Protein	16												
$C_3H_5O_3^-$†						28	28						
$C_6H_5O_7^{---}$‡													16
Dextrose mM/1§					5			8	56	56–111	56–167	111	111
mOsm/1‖	320	308	616	328	326	567	274	321	343+	335–390	320–431	400	402
Na:Cl	1.4	1.0	1.0	0.9	0.9	1.07	1.2	1.04	1.0	1.2	1.18	1.3	1.31
pH¶	7.45	5.0	7.2	6.8	6.8	6.5	6.3	7.1	6.9	7.35	7.6	8.1	8.4

* In each solution, the total milliquivalents of anions equal the total milliequivalents of cations.[22]
† Lactate.
‡ Citrate.
§ Dextrose, millimols per L.
‖ Total milliosmols per L.
¶ Values obtained in our laboratory.

expected, with resulting hyperchloremia and edema. The explanation for the development of hyperchloremia in six of twenty-one cases reported by Kop,[29] in which Kolff's solution was used, is not entirely clear, but possibly depends on the fact that the ratio of sodium to chloride of Kolff's solution is much lower than that of normal blood plasma. (Table IX.)

TABLE X

COMPOSITION OF VARIOUS SOLUTIONS USED FOR PERITONEAL LAVAGE

Solutes	Solution*									
	Ringer's	Locke's	Rhoads'[42]	Hartmann's	Modified Tyrode's I[18]	Modified Tyrode's II[20]	"A"[1]	Kolff's[28]	"P"[37]	Modified "P"[37]
NaCl	9.0	9.0	14.5	6.0	8.0	7.4	6.1	6.0	6.0	6.0
KCl	0.3	0.24	0.4	0.3	0.2	0.2	0.35	0.4	0.2	0.2
$CaCl_2$	0.25	0.42	0.2	0.2	0.1	0.2	0.23	0.28	0.1	0.1
$MgCl_2$					0.1	0.22	0.05		0.1	0.1
NaH_2PO_4					0.05		0.07		0.05	0.05
$NaHCO_3$	0.2	0.2			1.0	1.0	2.20	2.0	3.0	2.0
$NaC_3H_5O_3$			2.4† cc.	3.1						
$Na_3C_6H_5O_7.2H_2O$										1.57
Dextrose		1.0			1.5	10.0	10–20	10–30	20.0	20.0
Gelatin						10.0				

* Quantities represent gm. per L.
† Lactic acid.

Acidosis. There were thirty-two cases in which the value for the carbon dioxide combining power of the plasma was below normal. (Table VIII.) In one or more of these cases, one or another of seven solutions was used: 0.9 per cent solution of sodium chloride, Ringer's solution, Rhoads' solution, Hartmann's solution, modified Tyrode's solutions I and II, and "A" solution. This may be explained on the following basis: as has been pointed out in the preceding paragraph, with the exception of Hartmann's solution and "A" solution, the solutions listed contain a significantly higher concentration of chloride than blood plasma contains. Although in the case of Hartmann's and "A" solutions the concentration of chloride is not so markedly increased as in the other solutions, nevertheless both contain relatively high concentrations of chloride in comparison to the concentration of sodium, as indicated by the decreased sodium-chloride ratio. Although Rhoads' solution and Hartmann's solution each contains an adequate amount of sodium lactate, it is possible that the amount of lactate absorbed from the peritoneal fluid breaks down at too slow a rate to make available sufficient base to offset the loss of bicarbonate.

Edema. Further examination of Table IX reveals that in all cases in which the presence or absence of edema was reported, either pulmonary or peripheral edema was observed with the use of all solutions named except Rhoads' solution and "P" solution. Although 0.9 per cent solution of sodium chloride, Ringer's solution and modified Tyrode's solution I are essentially iso-osmolar with blood plasma, they already have been shown not to be in electrolyte balance in so far as chloride and base are concerned. It has been reported [14,19] previously that the blood plasma of uremic patients has an osmotic pressure higher than that of the blood plasma of normal persons. If this be true, the above three solutions, iso-osmolar

with normal plasma, become hypo-osmolar in the presence of uremia. The following solutions, although hyper-osmolar, likewise have been shown not be in chloride or base balance with normal plasma: 1.8 per cent solution of sodium chloride, Rhoads' solution and modified Tyrode's solution II.

Explanation is not at hand concerning why edema did not develop in the two cases in which Rhoads' solution was used. Nor is it apparent why edema developed in the case in which 5 per cent dextrose solution was used; one would expect the reverse to be true, since its use as a perfusing fluid experimentally and clinically[35,37] has been shown repeatedly to result in hypochloremia, hemoconcentration, symptoms and signs of clinical dehydration and shock.

The appearance of edema in cases in which Hartmann's solution was used may have been attributable to the fact that Hartmann's solution has an osmolar concentration of 274 as against 320 for normal plasma. (Table IX.) This discrepancy undoubtedly becomes greater in the presence of uremia.[19] Since Hartmann's solution appears to be otherwise essentially in equilibrium with normal blood plasma, the discrepancy could be offset by the addition of enough dextrose to render the solution hyperosmolar, as has been done in the case of "A" solution, Kolff's solution and the two "P" solutions. No explanation is offered on the basis of the composition of the dialysate for the appearance of edema in two of the cases in which "A" solution was used. The edema may have been attributable to hydremia induced by excessive parenteral administration of fluid, or to hypoproteinemia. In one case in which modified "P" solution was employed, a transient episode of pulmonary edema developed in the course of lavage. The cause for this episode appears to be clear and has been discussed at length elsewhere.[37]

The inaccuracy of the foregoing data is recognized, and probably, if similar data were available for all cases in the series, the figures would be somewhat different. Another factor in the inaccuracy of the data is the impossibility of estimating in all cases the effect on the blood values of parenteral administration of various electrolytes, notably solutions of sodium chloride and of bicarbonate or lactate. However, these data probably are sufficient to indicate the importance of using a carefully selected solution for lavage.

CHOICE OF SOLUTION

It becomes apparent that any solution, in order to be considered suitable as a perfusing fluid, should meet certain qualifications: (1) Its composition should be such that it will not alter the normal electrolyte pattern of the plasma and extracellular fluid. (2) It should permit maximal diffusion into it, from the blood, of nitrogenous and other waste products of a crystalloid nature. (3) Its tonicity should be such as to insure, in so far as possible, against water exchange across the peritoneum. In fact, the ideal fluid should be moderately hypertonic, for mild dehydration is much less hazardous and more easily controlled clinically than are excessive hydration and edema. (4) The solution should be as non-irritating to the peritoneum as possible, in order to reduce hyperemia and exudation, with consequent decrease in the efficiency of the filtering membrane. Although it is almost impossible to construct a solution of similar composition to normal blood plasma, five solutions appear essentially to fulfill the foregoing criteria: Hartmann's solution, Kolff's solution, solution "A" of Abbott and Shea, "P" solution, and modified "P" solution.

These solutions satisfactorily fulfill the first two qualifications. Hartmann's solution as such does not adequately meet the third requirement; but if, as has been said, sufficient dextrose is added to make a 2 per cent solution, its tonicity is sufficiently increased to make it adequate. In regard to the fourth requirement, any chemical solution introduced into the peritoneal cavity will induce some degree of irritation. This, however, can be kept at a minimum by buffering the solution to a pH approximat-

ing that of blood plasma. Rosenak[44] has stated that a solution which is too alkaline is as irritating to the peritoneum as one which is too acid. For this reason "P" solution was modified in an attempt to correct its high alkalinity (pH 8.1). It was found, however, that a solution even more alkaline was obtained; modified "P" solution has a pH of 8.4, making it necessary to adjust the pH to 7.5 with citric acid before use.

One observation in the case in which modified "P" solution was used raised a question as to the advisability of using this solution as a perfusing fluid. The return of the concentration of electrolytes of the blood to normal or near normal during the period of dialysis had led to the belief that modified "P" solution fulfills the criteria for a satisfactory irrigating fluid from the standpoint of electrolyte balance. However, the prolongation of the coagulation time of the patient's blood suggested that sufficient citrate was absorbed from the peritoneal cavity to alter significantly the coagulability of the blood.[37] Since this episode, however, this solution has been used in another case in which continuous lavage was carried out for ten days, with no detectable alteration in the coagulability of the blood.[36]

It will be noted that of the five solutions just mentioned (Hartmann's, Kolff's, "A," "P" and modified "P") only "A" solution and Kolff's solution approximate normal plasma in pH. Hartmann's solution, "P" solution, and modified "P" solution must be buffered with a suitable buffering agent to adjust the pH to 7.5 before they are satisfactory for use.

In most of the cases reported in the past three years penicillin has been added to the solution in concentrations of 5,000 to 25,000 units per L. in an attempt to inhibit bacterial growth and contamination of the fluid in the peritoneal cavity. As a result, the contaminating organisms usually recovered in the peritoneal fluid have been gram-negative organisms, resistant to the action of penicillin, such as Escherichia coli, organisms of the genus Pseudomonas and Aerobacter aerogenes. It appears that addition to the perfusing fluid of streptomycin, in a concentration of 20,000 units per L., may be indicated in an attempt to inhibit the growth of these organisms that are resistant to penicillin. Fine, Frank and Seligman[18] and others have added sodium sulfadiazine to their solutions in concentrations varying from 60 to 120 mg. per L. We have not added sulfonamide compounds to our solutions for peritoneal lavage because of the remote possibility of inflicting further injury on already damaged kidneys.

A sterile solution of heparin has been added in most cases to inhibit formation of fibrin on the peritoneal surface. However, Bloor and his co-workers[9] recently have reported that if rabbits are given heparin in large doses, intraperitoneal adhesions are as likely to develop after peritoneal injection of solution of sodium chloride or of gelatin as if the animals had not been given heparin. We have added heparin in the amount of 1 mg. per L. and have found that in this concentration it is not absorbed sufficiently to alter the coagulation time of the blood. Doenges and Strahan[16] added heparin to their solution in the concentration of 2 mg. per L. apparently without untoward effect. In our first case in which modified "P" solution[37] was used, the patient appeared more comfortable during the period of lavage than had two patients who previously had undergone lavage, and we were able to maintain a higher rate of flow without discomfort. We interpreted this as being attributable, possibly, to the influence of citrate in the perfusing fluid in inhibiting the formation of fibrin on the intestinal coils, with consequent decrease in the tendency to matting and channelling. In a later case[36] in which the same solution was employed, evidence of fibrin could not be demonstrated at necropsy either on the parietal or visceral peritoneum. It is possible that the addition of sodium citrate to the perfusing fluid, in addition to supplying necessary base, may be a more effective means of inhibiting formation of fibrin than is heparin.

Protein has been recovered from the per-

fusing fluid in sizable amounts and this fact, in association with decrease in the concentration of plasma protein, raises the supposition that the patient may lose protein from the plasma, across the peritoneum into the dialysate. Some have added gelatin[20] or substances of like nature to the dialysate for the purpose of raising the colloidal osmotic pressure of the dialysate in an effort to block loss of protein. The question whether protein molecules can diffuse across the peritoneum has been debated for a long time. Up to the present it cannot be said definitely whether protein actually is lost thus from the body during lavage or whether protein found in the irrigating fluid is a result of inflammatory reaction on the peritoneal surface itself. We have not added such substances to the perfusion fluid; but when the concentration of protein in the plasma has become significantly low, whether owing to loss of protein or to inanition, we have preferred replacement by parenteral administration of blood plasma, serum albumin or whole blood.

The method of preparation of solutions in general is governed by the physical characteristics of the apparatus to be used as well as by other facilities available. These details as well as the procedure itself and the indicated collateral therapy have been discussed fully elsewhere.[37]

TUBES

Many different types of tubes have been employed for introducing dialyzing fluid into the peritoneal cavity as well as for drainage. Rubber catheters, or glass or stainless steel tubes, with multiple perforations, have been used frequently as inflow tubes, whereas mushroom tip catheters of large bore, or stainless steel sump drains similar to the perforated suction tubes used in operating rooms, commonly have been employed as outflow tubes. In four previously reported cases[37] identical modified stainless steel surgical suction tubes were employed for both inflow and outflow. Although with these tubes it was possible to achieve reasonably satisfactory circulation of dialyzing fluid through the peritoneal cavity, nevertheless difficulty with leakage of fluid around the tubes and also with bacterial contamination of the peritoneal cavity continued. Leakage occurs probably because of relaxation of tissue of the anterior abdominal wall around the tubes, attributable partly to the fact that the rigid tubes must be introduced and fixed at an oblique angle, and partly to movement of the tubes from respiration and movements of the patient. Peritoneal infection may well be introduced around the tubes as well as through the air holes in the outflow tube, although great care has been taken in all cases to keep the tubes and the areas surrounding them as nearly aseptic as possible.

Recently, Rosenak and Oppenheimer[45] have described the disadvantages of using rigid tubes for peritoneal lavage and, in an attempt to obviate their disadvantages, they have devised a new type of tube, providing a rigid extra-abdominal portion and a flexible intra-abdominal portion. At the clinic we have used Rosenak-Oppenheimer tubes in one case and found the inflow tube to be entirely satisfactory. However, the flexible steel spring (closed coil) on the outflow tube appeared to be wound too tightly to allow free flow of peritoneal fluid through the interstices of the coil. As a result, we experienced considerable difficulty in withdrawing fluid from the peritoneal cavity, the abdomen became distended with fluid and leakage occurred around both the inflow and outflow tubes despite tight approximation of tissue around them.

Accordingly, we have devised a tube in which we have attempted to combine what appear to us to be the beneficial features of both the Rosenak-Oppenheimer tube and the surgical sump drain previously used, as well as to eliminate foreign-body reaction around the tubes. The details of construction of this tube are described elsewhere.[17]

Like Rosenak and Oppenheimer[45] we are of the opinion that inflow and outflow tubes, with a rigid extra-abdominal portion and a flexible intra-abdominal portion, are

superior to completely rigid tubes, and that such partly flexible tubes will eliminate most of the drawbacks listed previously. Although in Rosenak and Oppenheimer's hands the closed coil spring has served satisfactorily as a flexible drainage tube, our difficulty with that type of tube has led us to speculate as to whether a plastic tube might not be more advantageous. We have had an opportunity to try this tube clinically, and have found that it will provide easy drainage of fluid from the peritoneal cavity, with minimal leakage and risk of peritoneal infection.

Abbott and Shea[1] in their studies of intermittent lavage used a trocar through which a rubber catheter could be introduced for intermittent injection and withdrawal of perfusion fluid. As commented on earlier, Frank and his co-workers, previously strong exponents of continuous lavage, recently have reported on an additional series of patients, some of whom were given intermittent lavage through a single incision in the anterior abdominal wall in the hope of reducing the incidence of peritoneal infection thereby. As a means of decreasing leakage of perfusion fluid from the peritoneal cavity, the tube is introduced through an incision in the skin of the upper portion of the anterior abdominal wall and is passed along the subcutaneous tissues to the right lower quadrant, in which region, by means of a McBurney incision, the tip of the tube is inserted into the peritoneal cavity. Then the subcutaneous layers and skin, severed in making the McBurney incision, are closed tightly over the tip of the tube. The base of the tube is connected to the apparatus in much the same manner as were the two tubes which Frank and his colleagues used previously, and alternate filling and drainage of the peritoneal cavity is accomplished by means of a series of stopcocks as described.[20] Whether this procedure has sufficient advantage over methods currently in use for intermittent or continuous lavage to justify its widespread adoption can be determined only after further use of the method.

DURATION OF PERITONEAL LAVAGE

What determines the optimal length of time for peritoneal lavage? There is no definite answer to this question at present, and yet the question has arisen whenever peritoneal lavage has been carried out. In general, in the absence of complications which might necessitate earlier termination of the procedure, the attempt has been to maintain continuous irrigation until the level of urea (or non-protein nitrogen) in the blood falls to less than 100 mg. per 100 cc., until the excretion of urine in twenty-four hours exceeds 1,000 cc. in volume, or until the amount of urea excreted in the urine equals or exceeds the amount of urea excreted in the dialysate in the corresponding period of twenty-four hours.

Of interest in this regard are the curves of concentration of blood urea or non-protein nitrogen in the cases reported. Invariably, following cessation of lavage, concentrations of these substances in the blood increase gradually for several days despite daily increasing volumes of urine excreted, but ultimately the blood values for the substances named decrease again to normal or near normal levels. This apparently is because, despite the adequate volumes of urine excreted, the concentration of urea in the urine is not sufficiently high at the time lavage is discontinued to prevent a rather sudden secondary rise of the concentration in the blood. However, as has been said, the concentration of urea in the blood gradually decreases as its concentration in the urine increases.

HAZARDS OF PERITONEAL LAVAGE

From the foregoing review it becomes apparent that peritoneal lavage as a means of treating acute renal failure, accompanied by anuria and uremia, is not without certain hazards, and complications, many of which may be serious. Because of this, and since, if patients have advanced organic renal disease, lavage at best can lead only to temporary clinical improvement, its

use as a therapeutic measure should be restricted to cases in which acute renal failure is associated with reversible renal lesions.

Channelling and pocketing of the omentum and intestinal coils about either the inflow or the outflow tube, with disruption of the flow of peritoneal fluid and reduction of the dialyzing surface, constitute a further complication to the procedure. Perhaps reduction of the incidence of peritoneal contamination and infection, and addition to the irrigating fluid of increased amounts of heparin will, to a great degree, aid in combating this hazard. There is no doubt that intra-abdominal adhesions resulting from previous abdominal operations will aggravate and tend to promote such a disastrous development. Plugging of tubes, leakage around tubes, perforation of viscera by rigid tubes, and hemorrhage attributable to erosion of blood vessels by pressure from rigid tubes all are additional hazards which must be borne in mind.

The risk of lethal peritonitis, although small, nevertheless remains a factor with which to reckon. Peritoneal contamination appears to occur in a large percentage of cases even if a bacterial filter is used in the system. Whether or not the use of improved peritoneal tubes will reduce the incidence of peritoneal infection remains to be seen. There can be no doubt that the antibiotic agents, penicillin and streptomycin, added to the irrigation fluid and administered parenterally, are of the utmost importance in control of this complication.

Depletion of plasma proteins, sometimes to a critical level, may be a serious complication and contribute to the production of either peripheral or pulmonary edema. If significant hypoproteinemia appears imminent, replacement of protein by administration of whole blood, plasma or serum albumin may be indicated. Any such substance must, however, be used with caution.

Difficulties in the maintenance of adequate electrolyte and water balance on both sides of the dialyzing membrane constitute the greatest hazards. It has been shown repeatedly that this balance is extremely delicate, and parenteral therapy, or minor changes of technic or in composition of fluid may produce rapid and, in some cases, deleterious consequences. The complications of severe dehydration, depletion of electrolytes and overhydration, with massive peripheral or pulmonary edema, are of such magnitude that they must not be underestimated.

It has been well established that during the period of diuresis, following a prolonged period of anuria or oliguria, the renal tubules have not yet regained their ability to conserve salt and large quantities of sodium and chloride may be lost daily in the urine. During the period of peritoneal lavage the patient will absorb sufficient sodium and chloride across the peritoneal membrane to maintain essentially normal concentration of sodium and chloride in the blood. However, when this supply of salt is withdrawn due to cessation of the procedure, great care must be taken to supply adequate amounts of salt, either by mouth or parenterally, otherwise the symptoms and signs of deprivation of salt may ensue.

COMMENT

If the foregoing possibilities are borne constantly in mind, the results achieved often justify the risks involved. The procedure itself is basically simple and the apparatus can be constructed and assembled in any hospital. Facilities for preparing sterile perfusion fluid in large amounts must be available, as well as a clinical laboratory adequate for blood counts, chemical examination of the blood and the other indicated studies.

Experience with the procedure in the past twenty-five years has shown that it has a definite place in the treatment of acute renal failure. Peritoneal lavage is neither superior nor inferior to other methods of extrarenal excretion, such as external dialysis or continuous lavage of the gastrointestinal tract. Rather, it would appear that decision

as to the method of choice must be governed by the indications or contraindications of the case under consideration. If a patient recently has undergone an abdominal operation, peritoneal lavage undoubtedly is contraindicated. In like manner, infections of the skin of the anterior abdominal wall, extensive intra-abdominal adhesions as a result of previous abdominal surgery, or marked obesity of the anterior abdominal wall should be considered as contraindications.

When acute suppression of renal function with increasing renal insufficiency develops, conservative treatment, including supportive measures, should be employed for several days in an attempt to promote formation of urine. If, however, failure appears to be on the basis of a reversible lesion, if oliguria or anuria is prolonged, if symptoms and signs of uremia develop despite conservative measures and if the probability of recovery by conservative measures becomes less than the risk of extrarenal means of excretion, peritoneal lavage or one of the other means of extrarenal excretion should be initiated as a lifesaving measure.

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Seminars on Renal Physiology

Introduction to the Study of Renal Function*

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IT is now possible to measure a variety of discrete and specific renal functions in quantitative terms. Without such measurements many recent advances and numerous investigations relating to the role of the kidneys in the metabolism of water, electrolytes and a host of organic compounds ranging from urea to vitamins would have been impossible. Thus a great debt is due a handful of investigators for the concepts and technics that have placed investigation of renal physiology on a sound basis and have permitted such a rapid expansion of our knowledge in recent years.

Homer Smith in his recent lecture on Renal Physiology between Two Wars[1a] has so well reviewed the historical aspects of the subject that only the briefest comments will be given here. Slightly more than 100 years ago Ludwig[2] proposed that urine was formed by simple filtration at the glomerulus. In 1917 Cushny[3] presented arguments for believing that urine was the result of glomerular filtration and tubular reabsorption. Subsequently, Richards and Wearn[4] in their classic work demonstrated by actual collections of glomerular filtrate and tubular urine from frog kidneys that all substances studied, except high molecular weight materials such as protein, occurred in equal concentration in plasma water and fluid obtained from the capsular space of glomeruli, making allowances for the Donnan equilibrium. These facts proved that simple filtration takes place at the glomeruli. Then, by finding increasingly concentrated urine in samples collected in the distal parts of the tubules, evidence for tubular reabsorption of water was obtained. They were also able to demonstrate with these elegant technics that glucose is completely reabsorbed by the proximal convoluted tubules and that the distal tubules are the sites of ammonia formation and final adjustment of pH. Later similar although much less extensive and complete studies were made on mammalian kidneys.[5] That the renal tubules are capable of excreting organic substances such as phenolsulphonphthalein and phenol red was demonstrated a few years earlier by Marshall.[6,7]

Thus there has been obtained direct evidence in amphibia and some mammals that urine formation is the result of simple filtration at the glomeruli, followed by modification of the composition of the glomerular filtrate by tubular reabsorption and excretion. It is also evident that certain functions are the responsibilities of specific locations in the tubules. It seems a reasonable assumption that the locations and magnitudes of the various tubular functions are arranged in an orderly and definite fashion so as to endow the kidneys with an ability to vary, over a wide range, the volume and composition of their end product. In this manner the volume and composition of the body fluids are maintained in the face of many different and difficult circumstances. That structure and its attendant functions are varied on a grand scale to meet extremely diverse ways of living is illustrated by the studies on the comparative anatomy and physiology of the kidneys, so effectively presented by Homer Smith in his lecture on "Evolution of the Kidney."[1b]

Next, indirect technics that could be applied to the study of man were developed.[1c] Discrete renal functions that can be measured in man with considerable assurance

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include glomerular filtration rate, minimal effective renal plasma flow and maximum capacities for the tubules to reabsorb glucose (Tm glucose)* and to excrete diodrast or p-aminohippurate (TmPAH).

Ability to measure glomerular filtration rate is a prime requisite for the rational consideration of kidney function. It must be utilized in the calculation of tubular excretion or reabsorption. Its ratio to renal plasma flow, called the filtration fraction, is important in considering renal hemodynamics. Any serious study of mechanisms of electrolyte excretion must include the calculation of the amount filtered at the glomeruli.

Although evidence that inulin clearance is a measure of glomerular filtration rate in man is indirect, it is nevertheless extensive and convincing.[1c,8] Likewise the clearance of PAH (or diodrast) at low plasma levels appears to be an excellent estimation of the rate of plasma (and blood) flow to effective tubular tissue.[1d] The validity of this method has been placed on a sound basis by studies of renal extraction of PAH utilizing a catheter in the renal vein (9,10).

That the ability of the tubules to absorb glucose is limited to a finite value has been confirmed over a wide range of plasma glucose levels.[1e,11] Similarly, TmPAH or Tm diodrast† appears to be based on a finite transport system.[1e] These tubular functions, in normal subjects under ordinary conditions, appear to be reflections of the active tubular mass, and thus it is common and reasonable practice to relate other kidney functions to them. Normal values that have been established[1e] for these relationships and for the various discrete renal functions are shown in Table 1. The latter are usually adjusted to a standard surface area of 1.73 sq. m. The figures for males are larger than those for females and thus are listed separately. Different relative values are observed in infants.[13–15] Decline in the absolute values of kidney functions is observed in the older age groups although this does not occur in every individual.[16]

TABLE 1*
RENAL FUNCTIONS IN NORMAL SUBJECTS[1e]

	Male			Female		
	No.	Mean	σ	No.	Mean	σ
Glomerular filtration rate (GFR)	67	131	21.5	21	117	15.6
Renal plasma flow (RPF)	61	697	136	17	594	102.4
Filtration fraction (GFR/RPF)	61	0.190	0.0244	17	0.202	0.0310
Diodrast Tm (TmD)	40	51.8	8.73	14	42.6	9.46
Glucose Tm (TmG)	24	375	79.7	11	303	55.3
GFR/TmD	40	2.63	0.344	14	2.81	0.555
GFR/TmG	24	0.371	0.0563	11	0.395	0.0617
RPF/TmD	34	14.0	2.16	14	14.2	2.36
RPF/TmG	18	1.93	0.460	6	1.98	0.554

* Values corrected to surface area of 1.73 sq. m.

There are several technical details concerned with the measurements of the discrete renal functions that have considerable bearing on their interpretation. These measurements are usually made under standard conditions which include bed rest, performance in the morning and omission of breakfast. Values obtained under these conditions over a relatively short period of time are not necessarily representative of the individual's function throughout twenty-four hours. Indeed, definite diurnal variations in filtration rate and renal plasma flow have been reported for normal and diseased subjects at bed rest.[17,18] Furthermore, renal plasma flow may be affected by many factors including exercise[19–21] and emotion[1d] while glomerular filtration rate may be influenced by diet, hormones and other variables.

Administration of fluids to promote high urine flows to insure accurate urine collections is common practice in the performance of renal function tests. Although extremes of dehydration and hydration may alter

* Although reabsorptive Tms for a number of physiologically important organic materials have been established, that for glucose is the most thoroughly studied. Ideally, a substance whose reabsorptive mechanism is saturated at low plasma levels would be preferable. Such a substance would obviate the necessity of the large doses of fluid and chemicals required for measurement of Tm glucose of TmPAH.

† Currently, TmPAH rather than Tm diodrast is used as a measure of excretory capacity. The mean value for TmPAH in thirty-one normal subjects was 77.5 ± 12.9 mg. per minute.[12] Sufficient data on the comparison of glomerular filtration rate and renal plasma flow to TmPAH have not yet been published to permit a statement on the normal ratio value.

glomerular filtration rate and possibly tubular excretory capacity,[22,23] these functions appear to be unrelated in any direct fashion to rate of urine flow.[19] Nevertheless, studies on the role of filtration rate or other functions in electrolyte excretion are difficult to interpret when variables of unknown influence or importance are introduced by the experimental procedures. Such variables to be considered include administration of fluid to produce diuresis, intravenous infusions necessary for the functional measurements and emotional reactions to the procedures. Certainly it is ill advised to attempt studies on electrolyte excretion when filtration rate is measured by the clearance of such substances as mannitol* which causes an osmotic diuresis, or thiosulfate which, as an anion, grossly disturbs the ordinary electrolyte excretion pattern. Inulin clearance remains the method of choice for measurement of glomerular filtration rate.

It should be clearly recognized that all discrete renal processes are subject to functional control and variation. Renal plasma flow is perhaps the most variable, being readily influenced by activity and emotion. Even tubular capacity to excrete or reabsorb substances, being dependent on active enzymatic transport systems, may be subject to such influences as temperature. Tm glucose is apparently affected by insulin[25] and other hormones which include those from the thyroid,[26] anterior pituitary and adrenal cortex.[27,28] Excretory Tms are also subject to hormonal control.

With this background it is not a difficult task to interpret renal function in terms of normal structure. For it is generally accepted that the 2½ million nephrons that make up each kidney are so similar that measurements of overall functions are an accurate reflection of the individual nephron's activities as well. Although there are considerable variations of size among the nephrons, it has been shown by anatomic studies[29] that there is an excellent direct correlation between the size of each glomerulus and its attached tubule. Similarly, it has been shown on physiologic grounds[1e] that there is a rather precise balance between glomerular activity and tubular function, at least in so far as the transport of diodrast and glucose is concerned.

In normal subjects, then, variations in the absolute values of the discrete renal functions and in their interrelations in response to physiologic or pharmacologic stimuli can be interpreted with some degree of assurance. The ratio of filtration rate to renal plasma flow, the filtration fraction, is useful in assessing glomerular hemodynamics, while the relation of the renal plasma or blood flow to TmPAH may indicate renal hyperemia or ischemia. The ability to measure glomerular filtration rate with reasonable accuracy permits calculation of the amounts of materials filtered by the glomeruli and is a prime requisite for study of the mode of excretion of any substance.

The presence of disease, however, immediately places a number of difficulties in the way of simple interpretation of kidney functional studies. These difficulties are of two major types. First, since the methods of measurement are indirect, it is not always readily apparent whether or not a disease process has invalidated the usual meanings of a given function or relationship. Second, in organic disease the structures of the individual nephrons may be affected to such varying extents that values obtained for kidney functions no longer reflect what goes on in each nephron. The observed value, then, may be simply an overall average of grossly dissimilar units. Under such circumstances, interpretations of renal functional measurements must be made with caution. Homer Smith has reviewed the interpretation of measurements of filtration rate, renal plasma flow and excretory Tm in disease from a functional viewpoint[8] and Jean Oliver from the structural aspects.[30]

The most serious concern in the first category relates to the validity of the measurement of glomerular filtration rate in the

* Although a small moiety of filtered mannitol is reabsorbed by the normal tubule,[24] the reasonable correspondence between its clearance and that of inulin can still be used in this argument.

presence of disease. When tubular damage is acute and very severe, it is likely that some of the filtered inulin, whose clearance in the normal is the same as the filtration rate, diffuses back through the damaged tubular wall. This probably occurs in severe insults to the kidney, as in poisoning due to carbon tetrachloride[31] or other substances. Recently Raaschou has recorded one patient with pyelonephritis whose inulin clearance was 8 ml. per minute and another whose urea clearance was 6 ml. per minute but whose glomeruli were histologically intact at autopsy.[32] Fortunately, instances of these types appear to be quite rare and there is evidence to suggest that measurements of glomerular filtration rate are possible even in advanced renal disease. This is based mainly on the reasonably good agreement of simultaneously measured clearances of inulin and thiosulfate in a number of different kidney diseases.[33] In normal subjects the clearance of either substance is a measure of filtration rate. Inulin is a molecule many times the size of thiosulfate, and identical clearances would not be expected if either or both should be subject to back diffusion. Other evidence, based on similar reasoning, includes the finding of more or less equal inulin and mannitol clearance* in several disease states[34,35] and the maintenance of normal urea to inulin ratio in chronic glomerulonephritis and hypertension.[36]

The validity of renal plasma flow determination in renal disease can be checked, as in the normal, by observation of the extraction ratio of the substance being used for measurement. This is particularly important in patients with advanced structural damage in the kidneys and should be utilized occasionally as a safeguard against erroneous conclusions in the study of most renal diseases. Low extraction ratios have been observed in advanced renal damage due either to hypertension[37] or glomerulonephritis[38] but are generally normal in congestive heart failure[39] and in early nephritis[40] and hypertension.[37] Changes in filtration fraction in organic disease of the glomeruli may be due either to a greater organic barrier to filtration than to the passage of blood through the vascular channels, or to secondary or even unrelated hemodynamic factors. However, as Homer Smith has pointed out,[8] determinations of renal plasma flow based on rapid extraction of a substance by the renal tubules can only measure the flow to actively excreting tubule cells. Thus, the ratio of diodrast or p-aminohippurate clearance to the corresponding Tm gives a true reflection of blood flow to functioning tubules.

The chief concern in measuring maximum tubular capacity to reabsorb or excrete in patients with renal disease centers about the problem of achieving complete saturation of the transport system under study. In the case of an excretory Tm the load of material available for saturating the mechanism is dependent on the renal plasma flow to the tubules. It may be difficult or even impossible to provide a load sufficient for complete saturation, if the blood flow, either overall or to a number of individual nephrons, is significantly reduced. Further, since plasma flow and Tm are not measured simultaneously, there always remains the possibility that the administration of large amounts of material for the Tm measurement has caused renal vasoconstriction. In conditions such as congestive heart failure, it might be advisable to measure renal blood flow by the extraction technic during the actual Tm measurement. To calculate a reabsorptive Tm, however, the filtered load must be known and thus one is in a better position to evaluate whether or not the mechanism is saturated. If no change is reabsorptive (or excretory) capacity is observed at different loads, it is possible to be fairly certain that a "Tm" value has been achieved. But whenever filtration rate (or renal plasma flow in the case of excretory capacity) is reduced to very low values and when tubular function has not been greatly affected, inordinately high plasma levels will be required to produce the necessary load. If the renal disease is sufficiently advanced and if

* See footnote on page 80.

glomeruli and tubules of different nephrons are affected to different degrees, some tubules may never become saturated.

In such circumstances, the observed ratio of filtration rate to Tm is simply the average of many dissimilar units. But by observing the amount of substance transported by the tubules at various loads it is possible to determine the relative distribution of the various possible combinations of glomerular and tubular activities.[1e] Application of such titration technics, both for excretory and reabsorptive functions in hypertensive patients, have indeed shown that abnormal kidneys may contain a large proportion of nephrons with abnormal relationships between glomeruli and their attached tubules. This may occur before there is serious impairment of overall kidney function. Less complete studies have indicated a similar situation in chronic glomerulonephritis.[35]

There is another difficulty in the interpretation of the relationship between filtration and Tm value. Especially in disease, administration of large amounts of fluid and of the substance whose Tm is to be assessed may cause large changes in the filtration rate. Thus, during Tm glucose measurements in glomerulonephritis, considerable increases in filtration rate have been observed.[40] Conversely, TmPAH measurements may sometimes be associated with considerable decreases. Although under ordinary circumstances it appears that Tm is independent of changes in filtration rate, such large and acute variations during the procedure render interpretation of the relationships quite unsatisfactory at times.

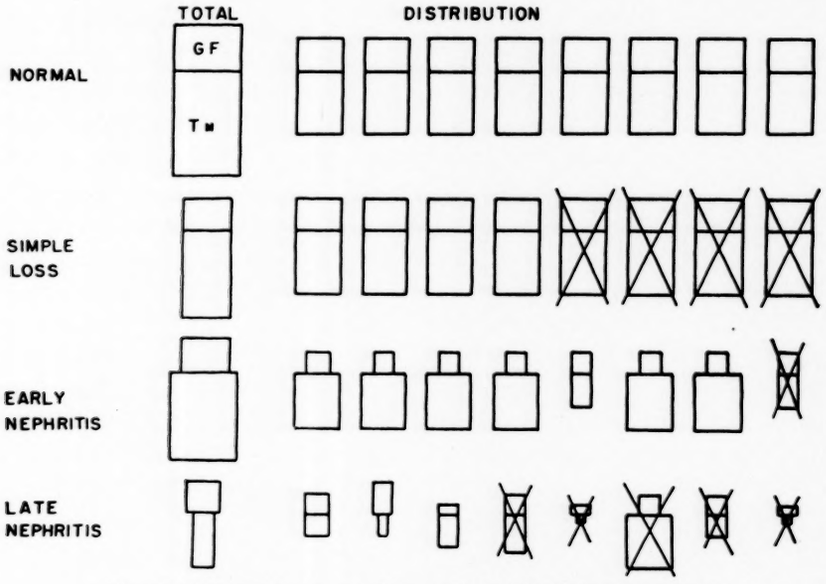

FIG. 1. Relation between glomerular and tubular functions.

Utilizing measurements of filtration rate and excretory and reabsorptive Tms, Smith[8] defines the following possible types of nephrons that may be present in renal disease:

	Filtration Rate	Tubular Excretion	Tubular Reabsorption
Normal active	Normal	Normal	Normal
Aglomerular	Absent	Present	.....
Impotent	Present	Absent	(Absent)
Inert	Absent	Absent	Absent

Provided that the various difficulties discussed previously can be discounted, it may be possible to detect the presence of a preponderance of one or another of the different types of nephrons. Nevertheless, before the functional tests can be translated into anatomic terms, strictly functional effects

and influences must be evaluated or ruled out. And, finally, it cannot be stressed too much that ordinarily we can measure only the overall average function of many nephrons which, in disease, may vary greatly among themselves, and indeed as Oliver has shown[30] may even have areas of hypertrophy and atrophy in the same tubule.

In spite of all the possible difficulties and complications, however, there is no doubt that measurements of discrete renal functions have been of great value in understanding how disease and disturbed physiology can affect the kidneys, and conversely, how disturbed renal function alters the volume and composition of the body fluids.

A very schematic representation of normal function is shown on the top line of Figure 1, glomerular function being indicated by the upper blocks, tubular function by the lower blocks. Individual nephrons, each with a glomerulus and its attached tubule, are represented by the row of similar units on the right. Although some nephrons are small and some are large, big glomeruli have big tubules and small glomeruli are attached to small tubules. The summation or average of the individual units is shown by the larger figure on the left.

Simple loss of the renal tissue is represented on the second line. Removal of one kidney would produce this pattern prior to the development of compensatory hypertrophy of the remaining kidney. A similar situation probably arises in the arteriosclerotic kidney in which whole segments may be destroyed with no damage to other regions, and possibly also in the infarcted kidney. Although total renal function may be considerably reduced, a fairly normal relationship between glomerular and tubular function is usually preserved in these circumstances.

Various clinical tests of renal function, such as PSP excretion, and urea and creatinine clearances are below normal. Ability of the tubules to form ammonia as a defense against acidosis may also be reduced.[41] Although no symptoms are to be expected under ordinary circumstances the kidneys, in consequence of reduction in total function, are unable to respond with normal facility to situations of stress, such as surgical operations, shock and serious infections. Nitrogen retention develops more readily than in normals, as do acidosis and alkalosis.

There are more serious consequences when renal damage involves an imbalance between glomerular and tubular function. An example of this is shown on the third line in Figure 1 such as may occur in acute glomerulonephritis. In this instance, glomerular filtration rate is depicted as being half of the normal, as it was in the example of simple loss of renal tissue. Few or no units may be destroyed but filtration rate is impaired more than tubular function[35] as measured by maximum ability to excrete diodrast (or PAH). Further, all units may not be affected to the same degree as indicated by the aberrant nephron. Occasionally, glomerular-tubular imbalance of this type may be shown with ordinary clinical tests. Thus, the urea or creatinine clearances, which are rough measures of glomerular filtration rate, may be reduced relatively more than is the excretion of PSP, a substance whose excretion is dependent on renal plasma flow and tubular function.

Reduction in filtration rate out of proportion to the reabsorptive capacity of the renal tubules for any particular substance will tend to cause retention of that substance. This mechanism may contribute to the sodium retention and edema of acute nephritis. But it must be remembered that the renal tubules have a wide variety of functions to perform, both reabsorptive and excretory. Even when glomerular damage appears to predominate, many observed abnormalities may be the result of concomitant damage to tubular function. Inability of the kidneys to concentrate, as well as impaired ammonia formation in nephritis, are undoubtedly due to tubular damage. These evidences of deranged function may occur when the maximum abilities of the tubules to excrete PAH or reabsorb glucose show little or no impairment. Con-

versely, it is conceivable that proximal tubular function may be considerably reduced with no evidence of abnormal distal function.

The terminal phase of any chronic renal disease is characterized by nitrogen retention. The clinical picture, however, may be quite variable, depending on the relative impairment of glomerular and tubular function. The situation in regard to electrolyte balance may be further complicated by involvement of extrarenal organs such as the heart and gastrointestinal tract. Thus congestive heart failure or persistent vomiting, both common in the advanced stages of renal disease, may singly or together contribute to the various abnormalities of electrolyte balance in these patients.

An example of terminal renal disease is shown on the bottom line of Figure 1. Many nephrons are destroyed while those remaining illustrate all possible combinations of glomerular and tubular impairment. As discussed earlier, Oliver's beautiful dissections and reconstructions of diseased kidneys indicate that the true situation may be considerably more complicated than shown in the diagram. Some parts of a single tubule may be hypertrophied while some parts are atrophied and others may appear normal.

Throughout the preceding discussion, the diagrams have been used as both anatomic and functional models. They are not, however, necessarily interchangeable. In addition to the effects of structural alterations of glomeruli and tubules caused by disease, the control of a number of renal processes may be disrupted on a purely functional basis. Interpretation of the effects of disease on electrolyte and acid-base balance is thus quite difficult, and knowledge in this important field can advance no more rapidly than permitted by progress in understanding normal controls of electrolyte excretion. Further considerations of these complicated processes are the subjects of two papers in these seminars.

In spite of the complex changes that may occur in the course of renal disease, a number of conditions are associated with fairly characteristic patterns of dysfunction.[42] Various authors have come to various conclusions[32,42–44] as to how much diagnostic value these patterns have. Although it must be confessed that especially when renal failure is advanced accurate diagnosis is sometimes impossible by any means, the present author believes that accurate analysis of kidney function not infrequently is an important diagnostic aid. At the very least such studies lead to a better understanding and evaluation of the patient. If performed at intervals, these measurements will yield valuable information on the directional trend and rate of progress of renal damage.

TABLE II
RENAL FUNCTION TESTS

Function	Specific Measurement	Clinical Test
Glomerular filtration	Inulin clearance	Creatinine clearance Urea clearance Plasma urea level
Renal plasma flow	PAH clearance	PSP excretion
Proximal tubule mass	Excretory—TmPAH	PSP excretion
	Reabsorptive—Tm glucose	
Distal tubule	Concentration—dilution	
	Electrolyte balance	
	Acid-base balance	
	Ammonia-forming ability	
Severe tubule damage and/or oliguria	(Back diffusion)	Urea clearance Plasma urea level

Measurements of the discrete and specific kidney functions are obviously more sensitive and accurate than some of the simple clinical tests. Nevertheless, it is hardly necessary to state that the latter can be very useful in evaluation of the functional status of the patient with kidney disease. The relations between the usual clinical measurements and certain discrete renal functions are shown in Table II. The methods for measuring specific renal functions shown in the middle column are those most commonly used today. The endogenous creatinine clearance at times is a fairly close measure of filtration rate.[45] Unfortunately, the methods of analysis are not entirely specific and there may be considerable discrepancies. For instance, in congestive heart failure the creatinine clearance is lower than that of inulin.[17] Nevertheless, the endo-

genous creatinine clearance represents a useful and simple routine estimation of filtration rate. The urea clearance also depends in large part on the filtration rate, but is lower due to passive back diffusion of urea through the tubular epithelium. The amount of back diffusion is variable and depends on the rate of urine flow,[46] the lower the urine flow the lower the urea clearance. As the filtration rate declines there may be a progressive increase in plasma urea and non-protein nitrogen concentrations. But these levels can be modified by dietary intake as well, and thus a precise relationship between renal function and plasma urea level cannot be established. Increases in plasma levels of substances such as phosphate, sulfate and potassium may also result from decreased filtration rate and may contribute to the development of acidosis and other symptoms.

Phenolsulphonthalein is excreted rapidly by the renal tubules[6] and, as the test is ordinarily performed, it is probably a very crude reflection of the renal plasma flow in patients whose tubular function is not greatly impaired. Since phenolsulphonthalein is excreted by the renal tubules, its excretion rate may be influenced by tubular function as well as by renal plasma flow. When kidney damage is severe, the phenolsulphonthalein excretion test is more dependent on tubular excretory mass than it is on plasma flow.

It is more difficult to assess distal tubular function in quantitative terms but it is probable that concentrating and diluting abilities are reflections of distal tubular activities. The ability of the kidneys to form ammonia is almost certainly a function of the distal tubules.

In the so-called "lower nephron nephrosis" there is actual necrosis of the renal tubular epithelium, which may follow a variety of chemical poisons or shock of various origins. The anuria or oliguria and retention of nitrogenous products and other substances, in this condition are due, in part at least, to back diffusion through damaged and inert tubular walls.[31] When there is oliguria even if only on a functional basis, the passage of urine down the distal tubules may be slow enough to permit a greater than usual absorption of urea and electrolytes, especially of sodium and chloride. This can lead to the retention of these substances in the absence of organic renal disease.

CONCLUSIONS

1. Discrete and specific renal functions can be measured and interpreted with accuracy in normal subjects. Such measurements include glomerular filtration rate, renal plasma flow and maximum capacity of the tubules to reabsorb and excrete organic materials.

2. These processes and their interrelations may be altered in disease by both functional and organic disturbances.

3. Although disease can produce very complex alterations in kidney structure, renal functional measurements may contribute considerable information useful in the understanding of disease mechanisms, clinical evaluation of patients and sometimes for diagnostic purposes. To achieve these objectives, however, careful evaluation of limitations and possible errors introduced by disease processes as well as those inherent in the technics themselves is essential.

4. Many substances share common pathways of transport, or at least are transported in the same anatomic areas. And there are many important interrelations in the consideration of electrolyte excretion and reabsorption. Nevertheless, it is important to carry over the concept of discrete renal functions to the study of renal mechanisms concerned with electrolyte excretion. This involves consideration of filtered loads, tubular reabsorption and possibly tubular excretion for each electrolyte individually. It is extremely dangerous to translate results with one substance to another, even when they may be as traditionally related in physiologic thinking, for instance, as sodium and chloride. Certainly there is no justification for assuming that a particu-

lar glomerular-tubular balance indicated by Tm glucose or Tm p-aminohippurate is a reflection of the ability of the tubules to handle any particular electrolyte. Analysis of component mechanisms is essential before generalizations or interrelations can be made.

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An Essay toward a Dynamic Morphology of the Mammalian Nephron*

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"We shall have occasion to suggest the analysis of physical entities into structures of events, and even events, as I shall try to show, may be regarded with advantage as having structure."

B. Russel[1]

"We may consider, therefore, organic form as an expression of a pattern of processes of an ordered system of forces. This point of view can be called *dynamic morphology*."

L. von Bertalanffy[2]

THUS from Parnassian heights speak the philosophers, and in laboratory and clinic the busy practitioners, "in perplexity and doubtful dilemma" before the enigma of structure and function that daily confronts them, take heart in their seemly endless effort of translating physical substance into dynamic activity. Of one thing they are sure: Neither the practical accomplishments nor the intellectual satisfactions so richly inherent in the method they follow can come to full accomplishment unless this dichotomy of structure and function is for the moment at least solved. There can be no "functional" answer to their problems standing apart from the "structural" explanation; like stereographic images the two must be fused for clear vision.† Since this is so, fortunate is he who has chosen the field of renal activity as his garden to cultivate, for no other organ offers as does the kidney in the complexities of its activity and its form so much for admiration and wonderment that yet remains reasonably within the capabilities of present day technics.

It will be apparent then that in a consideration of the activity of the renal tubule, although a morphologist may be helpful in various ways, first and foremost it is his part to determine if possible what it is that functions. The functionalist knows only what as blood goes into the conceptual area he calls a "kidney" and what as blood and urine comes out; the morphologist describes the physical aspects of the interim. On the framework of his description are fitted by inference observed dynamic events and this conceptual pattern must then be confirmed empirically by the observation of some specific and appropriate structural change. Such is the ideal accomplishment and in certain instances we shall see that it has been closely approached in achievement.

In simpler terms, the morphologist is to "localize function." In this endeavor there opens before him a series of isolable structures of infinitely regressing magnitude the

† The suggestion that the nervous system offers even more remarkable opportunities for correlation of structure and function will be admitted by all but to some will appear a counsel of perfection since its complexities seem at present to transcend resolution. It is an interesting point that both these biologic systems, cerebral and renal, are concerned with similar fundamental problems of living, namely, the adjustment of the organism to its environments and that they resolve it in converse ways. The nervous system modifies the organism and its behavior to fit the external environment; the kidney alters the internal environment to fit the organism.

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end of which in the light of his increasing technical ability is not in sight. Thus he localizes renal activity in the nephron and proceeds to glomerular filter and to tubule. In the latter he must distinguish between parts of tubule and, within any given part, differing segments. Passing to the cells of the tubule wall he comes upon membranes, both an internal (and one of these, "the brush border" of the proximal convolution, most remarkably differentiated in structure) and an external, the membrana propria, of simpler configuration. Within the cell he finds a whole hierarchy of cytoplasmic particulate bodies, batonets, "droplets," mitochondria and microsomes, again a series of decreasing magnitudes that seems limited in its members only by his ability to spin them out of his cytoplasmic suspensions, for the microsomes approach the limits of ordinary visibility and are not much larger than certain polymolecular complexes. All this variety of structure the morphologist can observe "before and after" the functional experiment and so point to physical alterations that have occurred for correlation with measured activity. But let us look at some examples for specific illustration.

One of the earliest of accurate and objective localizations was the demonstration in 1912 by Susuki[3] that dyes such as trypan blue or carmine are absorbed by the proximal convolution and stored in its epithelial cells. Susuki moreover noticed that the amount of dye absorbed and stored decreased as one departed from the origin of the tubule at the glomerulus; by means of the number of granules of dye seen in sections of its convolutions he divided this portion of the nephron into four segments. In 1915 dissections of vitally stained nephrons[4,5] confirmed the general inferences he had drawn from his study of sections; but when the proximal convolution was seen in its entirety, it was perfectly obvious that the distribution of dye indicated not that the proximal convolution is composed of segments but that in its handling of the dye it is a continuous functional unit in which exists a simple decreasing gradient of absorption. One might suppose from the appearance of this gradient that the whole length of the convolution was lined by functionally equivalent cells and that each had removed the same proportion of the total concentration of the constantly decreasing material that passed over its surface.

Another gradient of tubule activity demonstrable in the proximal convolution is similar in its distribution to the one just described for the dye. It has been quantitatively measured by a joint effort of functionalists and morphologists,[6,7] the former removing samples of tubule fluid from the proximal convolutions of small mammals and determining their sugar and creatinine content and the latter dissecting out the tapped nephrons, identifying the point of puncture and measuring its distance from the beginning and the end of the convolution. (Fig. 1.) It will be noticed that absorption by the tubule cells results in an evenly falling concentration of sugar so that most of it is removed by the time the first half of the convolution has been passed; similarly it can be shown that the greater part of the water of the original filtrate has been absorbed. Under physiologic conditions it is therefore apparent that the lumen surface of the cells of the terminal portion of the proximal convolution does not come in contact with any considerable concentration of sugar. If phlorhizin is given, the gradient of concentration of sugar in the tubule fluid is reversed and the terminal portion is flooded with a high concentration. (Fig. 2.)

It would appear therefore that there is a certain degree of similarity in the behavior of the cells of the proximal convolution in the handling of two substances as different as dye and sugar since under normal conditions the activity of the first part of the convolution is chiefly concerned with the taking up of the two absorbed materials. The conditions to which the cells of the terminal portion of the convolution are exposed in the two instances are, however, very

different. In the case of sugar, little if any remains for absorption by the time the tubule fluid reaches them, while in the case of the dye, which is continuously appearing in the urine, the cells are exposed to a certain concentration of it but do not take it up. As a matter of experimental fact it is impossible to fill these cells of the terminal segment by repeated injections of dye and its consequent excretion in the urine; it continues to heap up and accumulate in the upper part of the convolution until cell damage is evident but the terminal part remains, except for a few scattered granules, unstained.

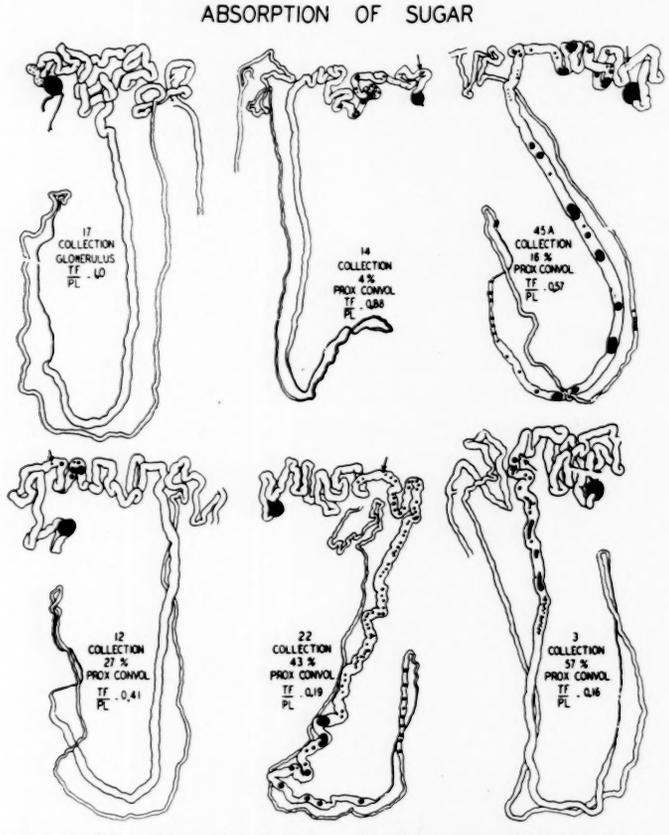

FIG. 1. The absorption of sugar by the mammalian nephron. The arrow indicates the point of puncture of the tubule; the black spots in the tubule are oil droplets injected to prevent retrograde flow of tubule fluid; × 14. (*Am. J. Physiol.*, 134: 562, 1941.)

The cells of the terminal portion of the proximal convolution therefore differ functionally from those of its upper portion in that they are unable to absorb the dye. The question arises, can they absorb sugar? The question is not open to direct examination in the experimental animal for this portion of the tubule lies too deep in the substance of the kidney to be reached by a micropipette. A morphologic approach can, however, give us at least indirect evidence for we have an opportunity to observe such a situation in human diabetes in which persistent glycosuria indicates that not only the terminal portion of the proximal convolution but also the whole tubule is being flooded with sugar solution.

It has been known since the late 1880's that great accumulations of glycogen may be found in the cells of the tubules of the kidney in diabetes. The significance of their occurrence, however, remained obscure since there was no unanimity of opinion as to just where in the course of the renal tubule they were situated. Microdissection

of such nephrons has localized these accumulations quite accurately; they are found only in the terminal portion of the proximal convolution.[8] All degrees of accumulation may be observed from that which produces only a slight irregularity in the contour of

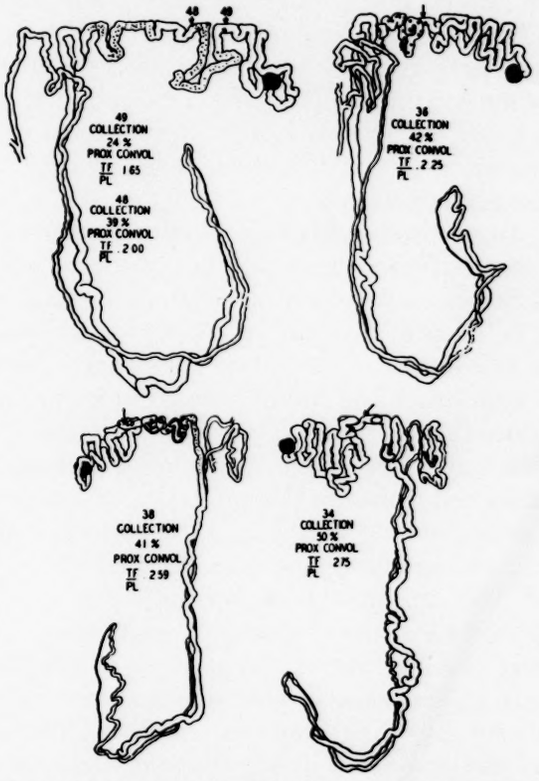

FIG. 2. The action of phlorhizin on sugar absorption; × 14. (*Am. J. Physiol.*, 134: 562, 1941.)

the tubule to the occurrence of great masses of vacuolar cells which distort its configuration into the most bizarre of patterns. Even in the most extreme examples, however, the upper portion of the proximal convolution remains undisturbed. (Fig. 3.)

Our modern knowledge of glucose-glycogen metabolism allows us, with the exercise of that considerable amount of inference which scientific custom tolerates in such quandaries, now to answer the question as to whether the distal segment of the proximal convolution can absorb sugar if it is available. Apparently it can for there is no other likely source of glycogen except the glucose of the tubule fluid.*

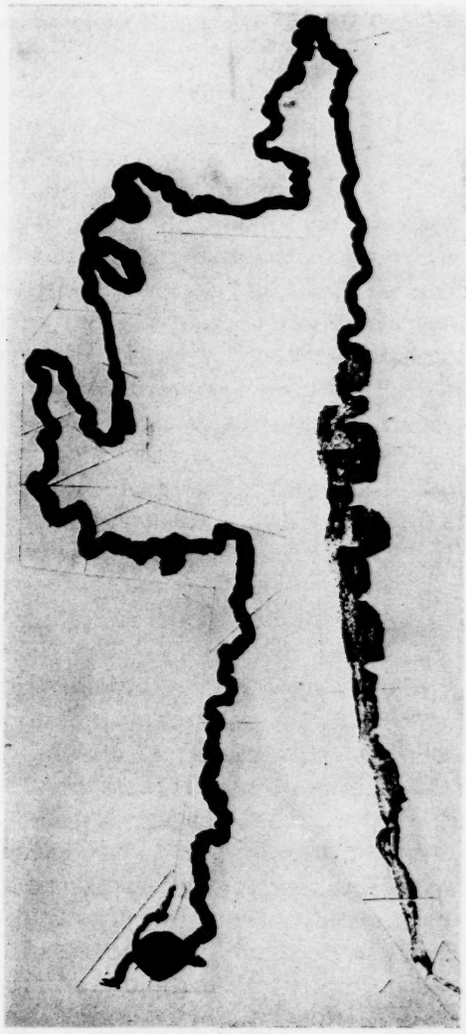

FIG. 3. Photomicrographic montage of proximal convolution from human kidney in diabetes showing the storage of glycogen in the terminal segment; iron hematoxylin stain; original magnification 150 × reduced to 28 ×. (*Harvey Lect.*, 40: 102, 1945.)

However, this conclusion does not mean that the function of the two segments even in the handling of sugar is identical. As I have stated, the upper convolution presumably continues to absorb great amounts in the diabetic and handles the excess in a manner at least compatible with its normal structure. The sugar absorbed by the lower segment is not passed on to the blood but is at least in part synthesized to glycogen and

* There is no other likely source unless one wishes to propose that for which there is no evidence and what would complicate our hypothesis beyond any reasonably credible limit, namely, that the cells of the upper proximal convolution absorb sugar from the tubule fluid and those of the lower segment secrete it from the blood.

accumulates within the cell to the point of its structural disruption. So the morphologic evidence strongly suggests a further functional differential localization, namely, the occurrence of two carbohydrate enzyme systems in the proximal convolution, the one in its upper portion having to do only with the absorption of sugar, the second in its terminal portion concerned with both absorption of glucose and glycogen synthesis.

The pattern of the gradients of absorption so far described seem reasonably comprehensible in that they are concerned with the continuous removal of a substance from a fluid which is passing down a tube. Absorption of another group of substances (namely, proteins) produces a less easily explicable pattern.

If a protein of moderate molecular weight, 70,000 or less, is injected intravenously or intraperitoneally, it appears in the urine and can under appropriate conditions be identified and so distinguished from the animal's own plasma proteins which may also be escaping at the same time into the tubule fluid. The glomerulus of the various species differs considerably in its permeability; and since that of the rat is so readily permeable that even his own proteins normally leak through and produce proteinuria, this animal is especially convenient for experimental study.*

If, therefore, a mixture of small proteins (e.g., egg white) is injected into a rat, "proteinuria" of almost pure egg white proteins occurs and the cells of the convoluted tubules are found filled with droplets.[9] Similar observations of droplets in the renal tubule after injection of various proteins have been made previously by many investigators (Gerard and Cordier,[10] Smetana and Johnson,[11] Randerath,[12] Rather[13]) but our particular problem is the exact localization of the process, first in relation to the proximal convolution and secondly to the structural organization of the absorbing cell.

In the isolated proximal convolution of a rat so treated is found a gradient quite different from any we have so far described. The droplets appear in moderate numbers at the origin of the tubule, then increase to a maximum and finally disappear before the terminal portion of the convolution is reached. The same type of gradient of absorbed protein droplets in the same portion of the convolution is found in the proteinuria following the repeated injection of the animal's own serum. (Fig. 4.) It would seem that a complex gradient of this sort must be due to the pattern of distribution of the absorbing cells for it is difficult to see how variation in the concentration of the material in the tubule fluid could produce it.

So far the gradients described have had to do with a fairly well defined physiologic process, namely, tubular absorption;† other

* The question of how permeable the human glomerulus is or, as it is usually put, whether the "normal" glomerular membrane of man leaks protein, comes down in the last analysis to a definition of what are to be considered the conditions of normal activity. Since a brisk walk may produce a slight proteinuria, it hardly seems that such can be considered frankly "pathologic." Moreover, as Addis has shown, the slightest protein leakage of the order of 5 mg./100 cc. filtrate at the glomerulus (and no other mammallian vascular membrane is so impermeable as this) would produce in man a loss of 9 gm. of protein in the urine in twenty-four hours unless it were absorbed by the tubule to the trace that is found in the urine. It would seem of necessity, therefore, that under every-day conditions of life protein is both filtered at the glomerulus and absorbed in the tubule and that the question as to whether these conditions are "normal" will concern only the idealist.

† It is common practice to distinguish sharply a great number of semantic abstractions in describing cellular activity in the renal tubule. The taking up and storage of dye or protein is "athrocytosis," sugar entering the cell from the tubule fluid is "absorbed" while urea "diffuses" back through the tubule wall. Phenol red is "secreted" from blood to urine, but the passage of neutral red in the same direction is by some mechanism apparently so inconsequential as to deserve no name at all. Doubtless all these concepts can in theory be accurately defined and justified, but it is certain that at best they constitute descriptions of a series of cellular activities in which various processes, such as the rate of transport through the cell and degree of metabolic alteration within the cell of the transported material, differ either quantitatively or qualitatively. An analogy drawn between the mechanisms of "athrocytosis" of protein and "absorption" of sugar would seem obviously forced. But how should the taking up from the tubule lumen of an amino acid be classified between such categories as athrocytosis and absorption? In the present uncertain state of our knowledge of renal tubule activity the morphologist will admit these terms have heuristic but not argumentative value.

gradients may be observed in the proximal convolution concerning which we are less well informed as to mechanisms and meaning. Fat, for example, occurs in the form of visible droplets in the cells of the normal

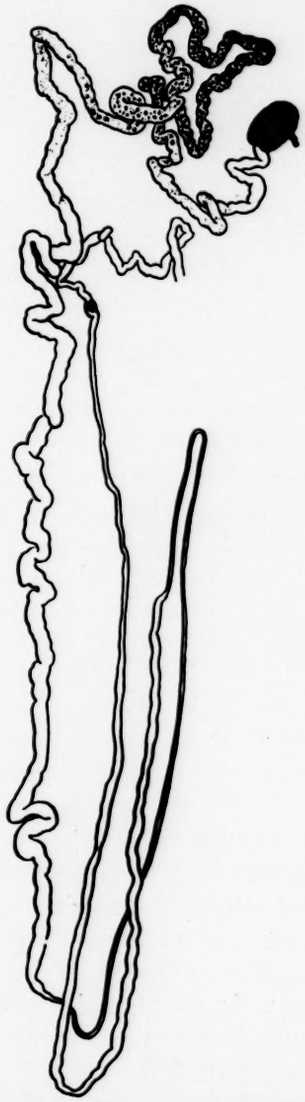

FIG. 4. Camera lucida drawing of rat nephron showing droplets of absorbed rat serum in the middle third of the proximal convolution. × 28. (*J. Mt. Sinai Hosp.*, 15: 175, 1948.)

proximal convolutions of some species. It seems likely in certain instances that this fat has passed from the blood capillaries to the renal cells as it does in other tissues and that the renal deposit is therefore part

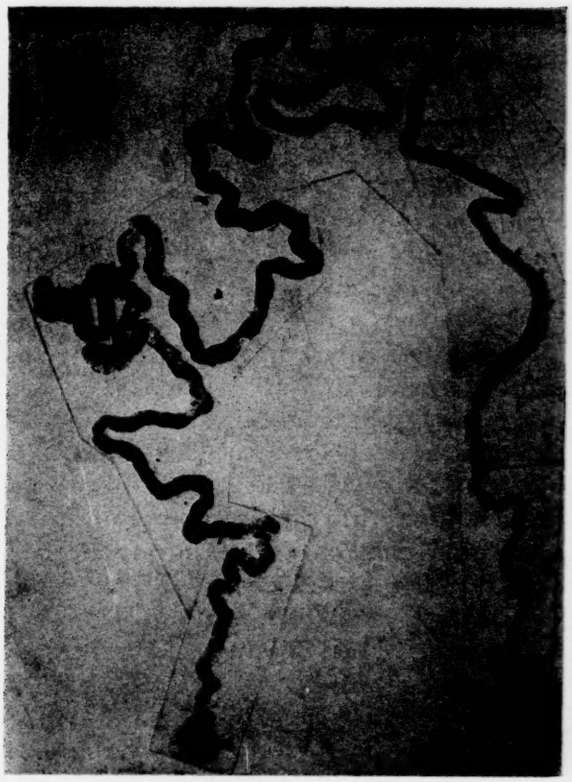

FIG. 5. Photomicrographic montage of a complete proximal convolution from a normal cat kidney stained with Sudan III. The fat droplets appear black and are concentrated in the middle third of the convolution; original magnification 100 × reduced to 30 ×.

of the general processes of normal fat metabolism. On the other hand, it is well known that under some experimental conditions lipids artifically introduced into the blood stream may pass through the glomerular filter and be absorbed by the renal cells from the tubule fluid, so that our interpretation of the mechanism of deposit in the normal animal is at best tentative.

Whatever its provenance a remarkable amount of fat is found in the proximal convolution of the normal cat, and in dissected specimens it is easily seen that the distribution of the droplets is similar to the gradient observed in the absorption of protein for its maximum of intensity is situated well down toward the middle third of the convolution and the terminal portion is regularly free of visible droplets. (Fig. 5.) In the normal dog much less fat is commonly present and this is uniformly limited to the terminal

segment of the convolution[14] and so resembles in its location the site of glycogen formation in man. The comparison of gradients similar in distribution affecting such different metabolic processes is mentioned since they are factual. What significance there may be in these coincidental localizations of protein-fat and carbohydrate-fat accumulation is problematic to say the least.

Very little is known concerning the localization of the fat deposition that is seen under abnormal conditions in the tubule of the human nephron. Only a few examples of "fatty kidneys" have been dissected; in these no uniformity of accumulation in any particular part of the nephron has been observed nor any deposit which from the regularity of its pattern might be considered a gradient. This does not perhaps seem surprising in those instances of renal damage in which the fatty change may be explained by the anoxia of ischemia but it was remarkable in one quite "genuine" case of "lipoid nephrosis," a condition in which some general pattern of metabolic or pathogenic disturbance is tacitly assumed, to find no morphologic pattern at all in the accumulations of the tubular fat.[8] A complete randomness of deposit was observed, however; the proximal convolutions were indeed most severely affected, but short stretches of tubule in all parts of nephron filled with fat droplets alternated with segments that were entirely free. Obviously we need more exact information concerning the "dynamic morphology" of the metabolism of fat in the nephron.

After this description of varying complex gradients in the proximal convolution it is perhaps well to close with an example which is in comparison relatively simple in its pattern. Such a one is that which is observed in the accumulation of minerals in the nephron, a process that may be very accurately and completely studied by the method of micro-incineration. The dissected nephrons are mounted on a glass slide and placed in a combustion furnace for 30 minutes at a temperature of 500°C. All organic material is destroyed and only the ash of non-volatile minerals, Na, K, Mg, Ca, remains adherent to the slide in the exact and recognizable pattern of the original nephron. The preparation is observed with dark field illumination.

In spodograms of dissected nephrons from the normal rat it is evident that it is the proximal convolution that contains the greatest amount of mineral. It is, of course, difficult in such preparations to judge accurately the concentration of mineral in the various portions of the nephron as the amount of tubular substance is greater in the thick proximal convolution than in the thin ascending limb of Henle's loop, although this source of error is less marked in the moderately thick distal convolution. However, when the concentration of mineral, as determined by chemical analysis, is greatly increased by the administration of vitamin D or parathyroid hormone, it is easily seen that there has been no significant increase in the amount of ash in any part of the nephron except the proximal convolution. In this segment there is no evidence whatever of any gradient of distribution; from its origin at the glomerulus to its terminal tip the spodogram is solidly caked with masses of mineral oxide. (Figs. 6 and 7.)

In the metabolism of water, carbohydrate, protein, fat and mineral it has been shown that the greatest intensity of the processes, at least as far as can be demonstrated by the methods of histochemical morphology, is located in the proximal convolution. A summary in diagrammatic and non-quantitative form of the various gradients is shown in Figure 8. This leaves the loop of Henle with its thin and broad portion, the distal convolution and the connecting tubule unaccounted for in our functional-structural synthesis, and these portions comprise the greater part of the total length of the nephron.

The morphologist at least can say nothing much about this considerable stretch of tubule for the simple reason that he does not see much happening in it. The func-

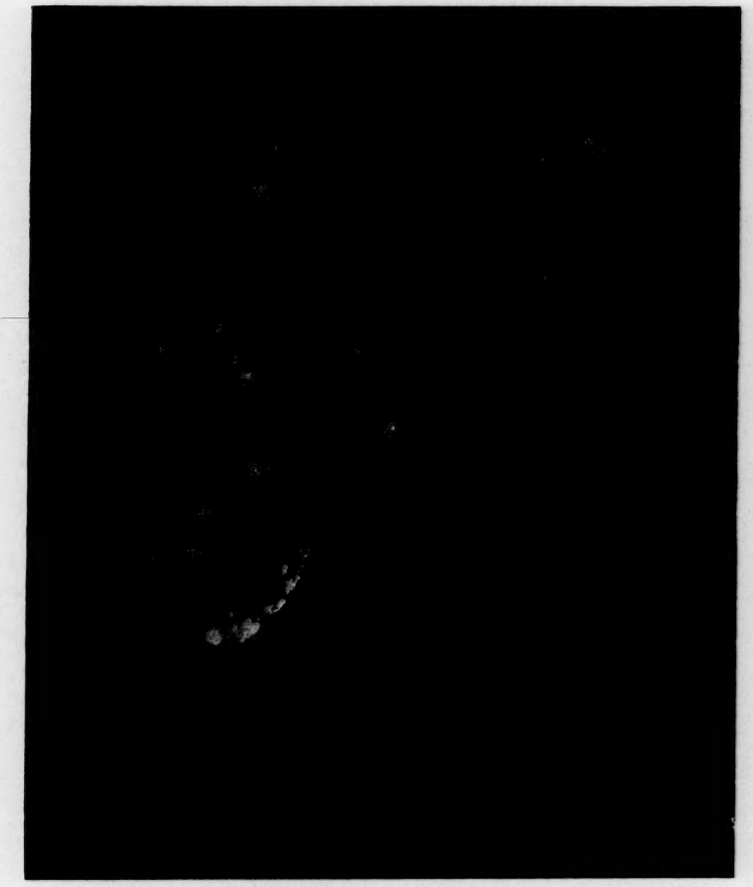

FIG. 6. Spodograms (montage) of proximal convolution (left) and ascending limb and distal convolution (right) from normal rat kidney; original magnification 100 × reduced to 25 ×.

tionalists have the negative evidence, arising largely from inability of the morphologist to contribute any positive information, that a certain process has not been localized in the proximal convolution; so they conclude that it must occur distal to this segment of the nephron. This would seem an exceedingly conservative use of the logical method but unfortunately the word "distal" has in our problem a double meaning. Besides its general usage of "further on" it also is the name of a specific portion of the nephron, the distal convolution or tubule. One is therefore at times uncertain when he is told that facultative water absorption or acidification of the tubule fluid occurs in the "distal tubule" whether *some* distal tubule or *the* distal tubule is meant.

In the case of the acidification of the tubule fluid we are fortunate since the color of indicators in the tubule fluid has been seen to change in the upper part of the ascending limb of Henle's loop and in the distal convolution of mammals in various sorts of experimental procedure.[15,16] This objective information along with certain indirect evidence drawn from pathologic material to be submitted later would seem to fulfill our requirement that both the functional and the morphologic aspect of a phenomenon be demonstrated before a conclusion is reached.

As to the absorption of the 20 or so per cent of water that must still be removed from the tubule fluid after it has left the proximal convolution before it becomes urine, the situation is not so clear. The loop of Henle since early times has been suggested as the important locus of absorption of water. The morphologist must admit

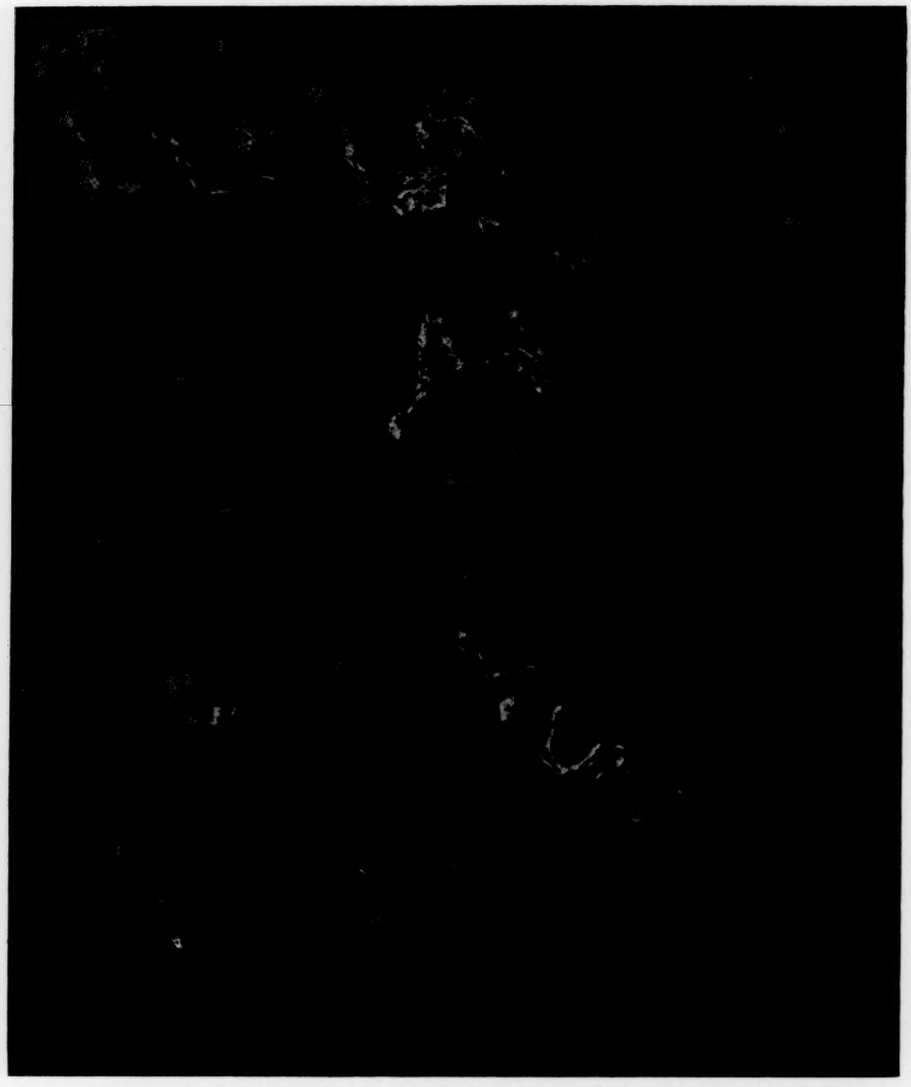

FIG. 7. Spodograms (montage) of ascending limb and distal convolution (left) and proximal convolution (right) from the kidney of a rat excreting large amounts of mineral after the administration of calciferol. Note the plate-like accumulations of mineral ash throughout the proximal tubule; original magnification 100 × reduced to 26 ×.

that it appears as if water might well be absorbed from such a long thin tubule lying in close proximity to capillaries, but he could also point out that its tenuous length might equally well be the fortuitous effect of architectural mechanical forces that draw it out and mold it into this configuration during the growth and formation of the papilla of the kidney. Moreover, not only must the distal convolution and connecting tubule be considered in this problem but also there is the whole system of collecting tubules from which water might be absorbed.[17] And what of the renal pelvis with its "pyelovenous return"? Perhaps it is as well that the morphologist is not tempted to a quick conclusion in the matter even from evidence that is particularly strong in its structural appeal. The loop of Henle *looks* like a good mechanism for the absorption of water and perhaps it does just this, but until the morphologist knows what is happening in the remainder of the urinary passages he remains prepared for any upset in his assumptions that may come when our knowledge of the unconsidered elements, collecting tubules and renal pelvis, is more completely developed.

We have seen so far the localization of various metabolic processes in tubules whose structural characteristics are normal; the morphologist as pathologist can also contribute information from instances in which frankly abnormal lesions have developed in specific parts of the nephron. Again it is the proximal convolution that stands out above all other segments as the one which reacts to the administration of toxic substances by the development of regressive change and cell death. This localization doubtless is determined by the fact that the functional mechanism produces the lesion, namely, by the absorption or, less likely, by the secretion of the toxic substance in this part of the nephron which so much evidence has marked as its most active part.*

It was Susuki[3] who first described the remarkable differences in the damage produced by the three heavy metals, chromium, uranium and mercury. He showed in histologic sections that potassium bichromate damages the first third of the proximal convolution, uranium nitrate its middle third and sublimate its terminal portion. These findings have been confirmed by dissection.[4,18]

While speaking of toxic damage that occurs in the proximal convolution reference might well be made to the cellular change noted in the renal tubules which was designated by the older pathologists as "parenchymatous degeneration." "Cloudy swelling" and "hyaline droplet" formation are commonly described as varieties of this pathologic process, the first being characterized by the development of fine granules in the cytoplasm of the renal epithelium and the latter by the accumulation of large "protein droplets." Both types of change are found in human kidneys at autopsy under conditions where various sorts of clinical evidence, often proteinuria associated with the presence of some renal toxic factor either known or suspected, indicate the renal lesion commonly designated by that etymologically absurd and conceptually obfuscatory term, nephrosis.†

The first of the "degenerations," cloudy swelling, in which the tubule cell is swollen and its cytoplasm finely granular, may no doubt occur as a bona-fide cellular lesion in various intoxications; but since it can be shown experimentally that its changes are accurately duplicated by postmortem alterations in as short a time as fifteen minutes, the practical pathologist quite properly tends to discount its significance in human postmortem material. Under such conditions it may be found in any part of the tubule of the nephron.

The occurrence of large "hyaline droplets" is quite another matter although the

* There are descriptions in the literature of acute toxic damage in all parts of the nephron, and it is common to find the ascending limb almost automatically included by pathologists when they describe in histologic sections a lesion in the proximal convolution. But the identification in histologic sections of these portions of the nephron is difficult enough under normal circumstances and quite impossible when pathologic lesions have altered their characteristic structure. Although no systematic study has been made in our laboratory of all the described lesions of toxic damage, in those that have been examined by dissection the structural lesions are, for all practical purposes, limited to the proximal convolution, provided there has not been a vascular disturbance associated with or part of the toxic action. This is frequently the case, especially when the toxic action is severe, and under these conditions damage may result by ischemia to any part of the nephron. This problem of ischemic damage and its relation to and differentiation from direct toxic action will be considered in more detail in a study of the lesions which develop in the nephron in conditions of shock that is now being prepared for publication.

† This curious barbarism was introduced by the clinician, Friedrich Müller, apparently because to his ear "osis" had the proper antithetical ring to "itis" and so seemed appropriate as a sort of counter-term to nephritis. The suffix "osis" had at the time an accepted meaning, "to be full of," as in lipoidosis or carcinomatosis, so that by all the custom and usage of medical nomenclature nephrosis means "full of kidney." On this etymologically nonsensical basis an elaborate superstructure of vague and varied conceptual meaning has developed, not surprisingly, so that in the end the word has come to be a mere label appropriate to its user's ignorance of what he is talking about. Thus proteinuria of unknown mechanism associated with edema, the complex structural damage that occurs in the kidney in shock, an obscure disturbance of calcium metabolism showing excess mineral excretion or the entirely normal absorption and storage of hemoglobin by the renal cells are all "nephroses." If all that is desired is to say that one is uncertain but suspects something is wrong with renal structure or activity, nephropathy is a word that at least is not *per se* ridiculous. Yet clinical authorities, agreeing entirely with these animadversions, insist that the term nephrosis is too well "established" to be discarded. At least one should realize that he can use the word nephrosis in only one of two manners, either cynically or naively, and neither attitude seems appropriate to the intellectual dignity of the science or the art of medicine.

older teaching of Fahr[19] described them as a second stage or "chronic" form of the small granules of cloudy swelling. They are the result, not of "degeneration" if by that term one means a lessening or perversion of activity, but of the normal protein ab-

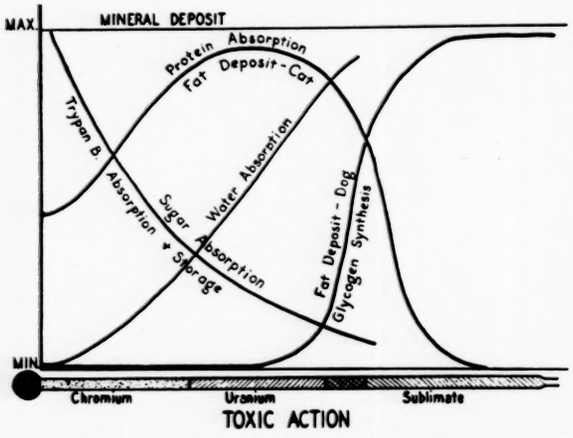

FIG. 8. The location and distribution of gradients in the proximal convolution.

sorptive and storing capacity of the cells of the proximal convolution that we have previously described. Unpublished experimental evidence has shown that such factors as time and protein concentration are required for the formation of visible droplets in the absorbing cells. Their absence therefore does not mean that protein is not being absorbed. Their presence is direct evidence of a functional integrity of a sort in the renal cells, and indirectly, in most instances at least, they indicate that an increased permeability of the glomerular membrane exists.

The long-continued and excessive absorption and storage of protein can lead, however, to the development of cellular damage and even to what properly may be called a chronic tubular nephropathy. This is a very common, spontaneous lesion in old rats[20] for these animals have a normally permeable glomerular membrane and a consequent physiologic proteinuria.[21] Severe tubular lesions with marked architectural change in the nephrons also result from the "nephrotic episodes" of glomerular nephritis or as a result of the proteinuria of the amyloid kidney. In all these conditions the fundamental mechanism of the tubular change is an overloading of the cells of the proximal convolution with protein, a resulting intracellular "indigestion" and consequent death and desquamation of the renal cells which, carried by the current of the tubule fluid, lodge in the distal convolution. We shall return later to the resulting architectural changes that result in this portion of the nephron.

A more detailed consideration of the hyaline droplets of absorbed "protein," whether normal or abnormal, seems warranted at this time for a closer examination of them shows that these objects are much more complex in their chemical structure than has previously been suspected. They, as well as the other particulate bodies of the cytoplasm of the cells of the proximal convolution, the mitochondrial rodlets and the smaller microsomes, may be isolated and subjected to biochemical analysis by grinding up the renal cells and preparing pure suspensions of the various particles by differential centrifugalization and other procedures. Work in progress[9] has shown that the intracellular droplet of "absorbed protein," egg white for example, is in fact a complex structure that contains only a relatively moderate amount of egg white proteins and a greater amount of ribonucleic acid and other cytoplasmic constituents. Morphologic evidence shows these substances to be derived in large part from the dissolution of the mitochondrial batonets of the renal cells. Similar cytologic changes are found in the absorption of amino acids by the renal cells of the proximal convolution.

Apparently, therefore, what is being seen by the morphologist in "droplet" formation is the structural aspect of the mechanism by which the enzyme-containing and energy-rich cytoplasmic elements of the renal cells combine with and metabolize absorbed proteins and amino acids. A great amount of biochemical evidence indicates that processes involving both synthesis and degradation of these substances occur in the kidney, so that the morphologist as he sees the mitochondrial rodlets dissolve and the "protein droplets" form, then disintegrate and finally disappear can perhaps

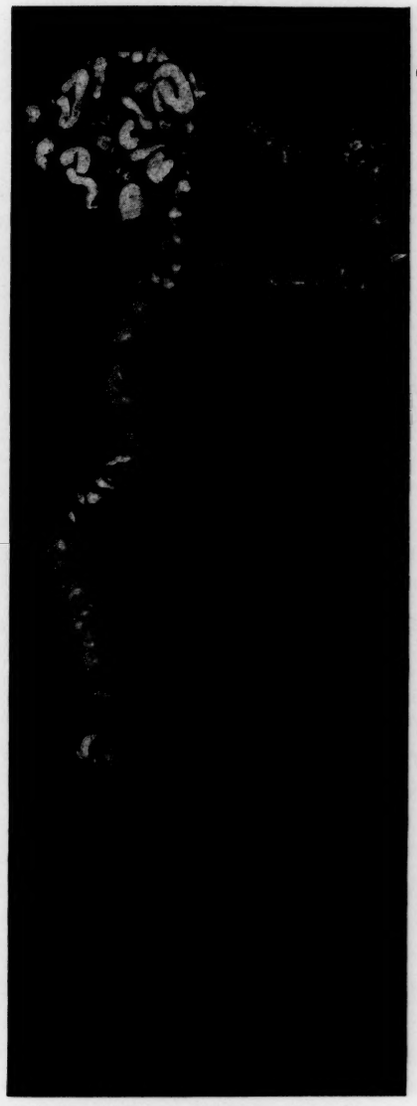

FIG. 9. A hypertrophied nephron from chronic glomerular nephritis. Note that in comparison with the normal nephron of Figure 10 the greater part of the hypertrophy is located in the proximal convolution; × 15. (Courtesy of Paul B. Hoeber-Harper Bros.)

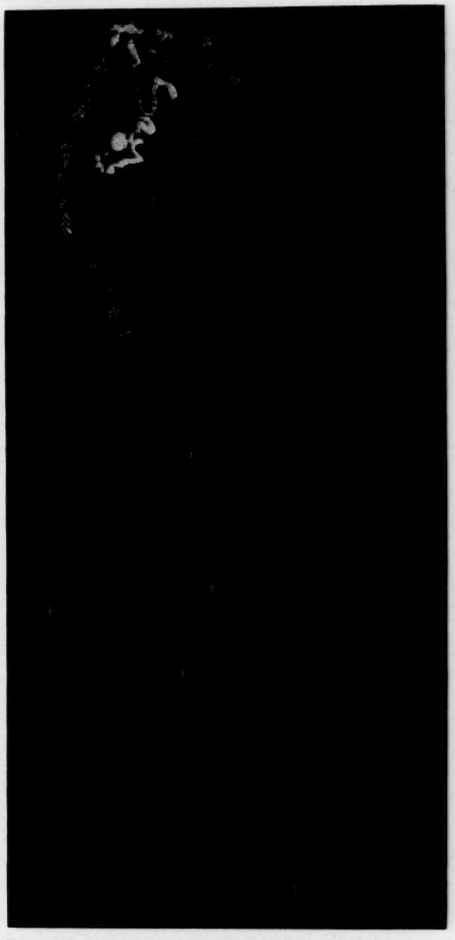

FIG. 10. A normal nephron from the human kidney; × 15. (Courtesy of Paul B. Hoeber-Harper Bros.)

believe that he has at least localized if not elucidated the metabolic process in the most minute of the cytologic elements of the renal cell.

To return to the localization in the tubule of the nephron of pathologic change that is dependent on the function of the involved part, another example is found in the mechanism of cast formation. The classic description of the location of casts in the lumen of the tubule as they are seen in histologic sections gives the impression that they may form in any part of the nephron. In dissected material it is evident that although disorganized debris and desquamated epithelial or red blood cells may be found throughout the tubular system from the glomerulus to the papilla, rarely if ever are formed consolidated casts seen except in the distal convolution, the connecting tubule and in the collecting tubules.[22] There is one exception to this rule, namely, the occurrence of casts of Bence Jones protein which may form as high in the nephron tubule as the proximal convolution.[8]

The coagulation of proteins is the fundamental mechanism in the formation of casts, and by this coagulation debris, fatty material and even desquamated epithelial or red blood cells may be incorporated into

the cast structure. The iso-electric point of the protein, the pH of the tubule fluid, its electrolyte content and the dispersive effect of urea are well known factors that influence protein coagulation, and it is in the distal convolution that the proper equilibrium

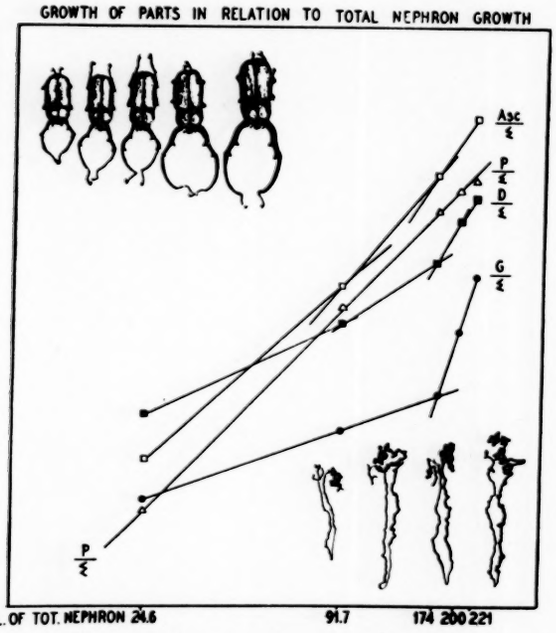

FIG. 11. Heterogonic normal growth of proximal convolution in rat kidney. The volume of the various portions of the nephron are plotted logarithmically against the volume of the entire nephron. Only the proximal convolution (P/Σ) fulfills the straight-line requirement of heterogonic growth.

for its occurrence is attained. That Bence Jones body coagulates in the proximal convolution becomes explicable, therefore, by the fact of its high iso-electric point. However, another substance, first described by Moerner[23] in normal urine, later found by Addis[24] in hyaline casts and then demonstrated in dissected normal nephrons to be concentrated in the tubule cells of the distal nephron,[8] seems essential to coagulation and definitive cast formation. As to what this substance may be, the morphologist can state only that it is metachromatic in its reaction to toluidin blue as he sees it in both renal cells and casts and that Moerner considered it to be chondroitin-sulfuric acid.

However uncertain the details of our knowledge of the exact mechanism of cast formation, enough is clear to explain why these structures are found only in the distal convolution and the collecting tubules. Those which form in the lower collecting system may flush out into the urine and therefore be both innocuous to the patient and helpful to the physician; those in the distal convolution are more likely to stick and it is to the result of this blockage that a great part of the architectural change of chronic renal disease is due.[22]

A final example of structural change in the tubule of the nephron occurring under pathologic conditions may be cited by the morphologist in explanation of his inability to demonstrate as elaborate a picture of structural-functional correlation in the distal portions of the nephron as he could in the proximal convolution. It will be recalled that he has repeatedly implied that this might be due to the essential facts of the situation, a lack of structural reaction truly correlating with a corresponding functional mediocrity. Such a conclusion is considerably strengthened by what he observes happening when the full load of renal activity is thrown upon a reduced number of nephrons. The functional result of the "compensatory" hypertrophy that develops may be entirely adequate either when nephrons have been destroyed by chronic renal disease or after surgical or experimental nephrectomy. The tubular mass of the kidney, using the term in the old-fashioned newtonian sense, increases, but this increase cannot be truly measured by the weight of the kidney or even by that of a single nephron if one were isolated and weighed for all parts of the tubule have not grown in response to the work stimulus to the same degree. Figures 9 and 10 show a hypertrophied nephron from a kidney of chronic glomerular nephritis and a nephron from a normal kidney; it is evident that the increase in mass is much greater in the proximal convolution than in the remainder of the nephron. Similar results are obtained in experimental compensatory hypertrophy[25] and the conclusion is thereby forced on a morphologist that the greater part of the work of the kidney is performed by that part which has preferentially responded to

the growth stimulus. In fact, the normal growth of the individual by increasing the metabolic load on the nephrons as he increases in size performs the same experiment for it has been shown[8] that the nephron under normal conditions grows irregularly in its parts. The loops of Henle and the distal convolution increase by the ordinary laws of growth increment, but the proximal convolution shows that peculiar form of exponential increase commonly found in hyperactive parts and which Huxley[26] has termed heterogonic growth. (Fig. 11.)

The examples of structural-functional correlation that have been cited will be sufficient to indicate that although morphologist and functionalist are perhaps separated by that ineluctable barrier which seems to cut through all aspects of human thought and endeavor with a resulting disrupting duality of expression and concept, nevertheless it is not a wall that stands between them but rather a transparent or at least translucent screen through which each can dimly see what his neighbor is doing. Nowhere as in the study of renal activity are the possibilities of such a meeting of minds more clearly promised for in the quite untranslatable words of Fritz Kühn,[27] "Die alten Anatomen nannten die Niere das *viscus elegantissimum*, das eleganteste Eingeweide, und das ist es in der Tat. Von äusseren Anblick bis in die letzten mikroskopischen Feinheit übertrumpft die Niere die andere Organe durch ihre Fülle an ästhetischen Motiven und durch die Eleganz, mit der in ihr die konstruktiven Probleme gelöst sind."

Such terms will not seem extravagant to those who know the form and beauty, redundant words, of structure and function in this *viscus elegantissimum*.

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Combined Staff Clinic

Mechanisms of Ascites Formation

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. FRANKLIN M. HANGER: We can define ascites as a collection of free serous fluid in the peritoneal cavity. In clinical diagnosis it is a routine discipline to associate ascites with certain disorders such as cardiac insufficiency, certain forms of renal disease, abdominal neoplasms, cirrhosis of the liver, tuberculosis and other inflammatory conditions of the peritoneum. In addition there are certain miscellaneous conditions which simulate ascites, namely, massive hemorrhage into the peritoneum, extravasations of urine following ruptured bladder, ruptured abdominal cysts, etc. Unless all these possibilities are carefully considered in every case of ascites grave errors in management may be committed. For instance, I recall a number of patients with ascites who, from the dilated venules of the face and alcoholic history, were assumed to have cirrhosis. However, rectal examination, lamentably deferred, revealed nodules in the peritoneum indicating that the ascites was due to malignancy.

In modern medical thinking the occurrence of ascites in these different clinical entities must be considered from the point of view of disturbed physiologic mechanisms. What happens in malignancy to bring about the development of ascites? What happens in cardiac disease? What happens in cirrhosis?

We know that in cardiac failure edema formation depends not only upon increased back pressure in the vascular channels but also upon a number of profound physiologic disturbances in the kidneys and other organs. Today we are going to use disorders of the liver to illustrate some of the disturbances which in like manner lead to retention of body fluid.

We will first consider the mechanical or circulatory factors in the causation of ascites. It is natural to assume that when the portal blood has difficulty flowing through the liver there is an increased back pressure and secondary portal hypertension. Normally the pressure in the portal vein is about 80 to 120 mm. of water; in many cases of cirrhosis of the liver, however, the tension rises to 300 or 400 and even 600 mm. of water. This stasis no doubt is conducive to extravasation of fluid into the peritoneal cavity but the chief clinical importance of portal hypertension lies in the development of a collateral circulation rather than in the production of ascites. Bleeding from esophageal varices or from dilated veins in other parts of the gastrointestinal tract is one of the great menaces of cirrhosis of the liver. Also portal hypertension causes changes in the spleen. The spleen enlarges, hypertrophies and undergoes structural metamorphoses that lead to hyperfunction of that organ. Thus, disease of the liver may, by causing hypersplenism, indirectly invoke the Banti syndrome of hypochromic, microcytic anemia, usually with low white blood count and low platelets. Sometimes abnormal globulins are demonstrable in the serum by various flocculation tests and occasionally, but not very often, increased hemolysis due to hypersplenism.

If the portal vein is occluded suddenly, the animal or patient frequently dies. Acute thrombosis of the portal vein is a very serious condition. However, if the occlusion is gradual, over ten days or more, a col-

lateral circulation is established without untoward effects and without the production of ascites in the healthy animal. When, on the other hand, the hepatic veins are ligated, which is technically difficult, or if the vena cava above the liver is occluded, a different picture is produced. The animal very rapidly develops ascites and even before ascites appears the lymph flow from the liver increases as much as twenty-fold. Sometimes, according to Volweiler[1] 10 per cent of the animal's body weight is secreted as liver lymph in a day. Likewise in experimental cirrhosis the lymph flow from the liver may be tremendously increased and it is possible that the factor of hepatic lymph flow may be the deciding one in determining the presence or absence of ascites in hepatic disease. Thrombosis of the portal vein or of the hepatic veins is encountered clinically. The latter condition, known as the Chiari syndrome, gives rise, as in experimental ligation of the hepatic veins, to marked ascites.[2] Narrowing of the hepatic veins brings about somewhat the same effect. Growing tumors impinging on the afferent vessels probably give rise to ascites more readily than other types of neoplasm within the abdomen. Of course, tumors may also induce ascites by compressing the lymphatic drainage of the splanchnic system, while others are intrinsically irritating to the peritoneum and invoke inflammatory reactions, thereby augmenting the extravasation of fluid into the peritoneum. Increased systemic venous pressure due to right heart failure produces somewhat the same effect. In chronic passive congestion not only is there increased back-flow of lymph from the liver but the stasis of blood causes a characteristic necrosis of liver cells in the center of the lobules. If hepatic injury is extensive, the capacity of the liver to maintain normal serum albumin levels is impaired. Hypoalbuminemia, due to hepatic insufficiency or following massive hemorrhage, when accompanied by venous stasis is much more conducive to ascites formation than either condition alone.

Whether the narrowing of the hepatic vascular bed in cirrhosis is the cause of portal hypertension is something of a moot question. A number of workers, one of the more recent being Dock,[3] have perfused cirrhotic livers, including postinflammatory cirrhosis and alcoholic cirrhosis, and have not found the flow of perfusate as restricted as would be expected if the obstruction were purely mechanical. However, when Dock perfused these diseased livers simultaneously through the portal vein at a pressure of say, 20 mm. of mercury, and through the hepatic artery at 100 mm. of mercury, thereby creating arterial and venous pressures in their more or less physiologic relationship, he found that the amount of blood flowing through the portal vein was diminished. This observation indicated to him that there is a rich anastomosis between the portal venous bed and the hepatic arterial bed in cirrhotic livers; and when the hepatic pressure is increased, there is interference with portal blood flow. This concept must be evaluated in terms of recent *in vivo* studies on the flow of blood through the liver.

Formerly anatomists injected portal veins and hepatic arteries with various waxes or collodion preparations to note where these two systems join in the liver. These preparations indicated that the chief area of anastomoses was in the region of the smaller bile duct system. However, Knisely[4] has recently developed technics for studying the mammalian liver under direct visualization and has prepared very beautiful demonstrations showing branches of the hepatic artery actually communicating with the sinusoids of the liver. He has also shown that these anastomoses are not constant. The lumens of the hepatic arterioles are continually changing. Sometimes no hepatic blood communicates with the sinusoids and at other times pure arterial blood enters the

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portal system and rushes through the sinusoids with actual arterial pulsation. It is obvious that studies on non-viable material do not reflect the circulatory status of the liver of the living animal. Knisely has estimated that under normal conditions 90 per cent of the blood flowing through the liver may be either arterial or portal, depending upon the time of day and the various physiologic conditions. The demonstration of a rich anastomosis between hepatic artery and portal vein gives us a theoretic mechanism, at least, for what we might call "functional portal hypertension." Indeed, I have seen cases of portal hypertension of several hundred millimeters of water in which biopsies of the liver and even postmortem examination have not revealed an organic cause for obstruction in the portal system. Much more study of the mechanisms regulating blood flow through the liver in health and disease is needed before this aspect of the problem can be discussed rationally.

Bradley[5] has shown that when the intra-abdominal pressure is increased the blood flow through the liver, normally about 1,500 cc. per minute, is diminished. The pressure exerted by massive ascites upon the vessels bringing blood to the liver not only reduces the blood flow through the liver but affects adversely cardiac, renal, respiratory and digestive efficiency. It is imperative to use all measures to prevent the development of ascites, or once present, to prevent secondary harmful pressure effects. Paracenteses should be repeated as often as is necessary, despite the loss of proteins of which the patient is already depleted. Repeated taps seem usually to be the lesser of the two evils.

In summary, we may say that although portal hypertension is very much in our thinking as a cause of ascites, portal stasis is probably not solely responsible for accumulation of fluid in the peritoneal cavity. Compensatory mechanisms are adequate with a healthy liver, with a healthy peritoneum and with normal plasma proteins to prevent the formation of ascites, even with complete occlusion of the portal vein. If, however, with portal hypertension other disturbances are superimposed, we find it a contributory factor which at times justifies surgery to shunt the overdistended portal vein into the caval system. In rare instances relief of ascites can be attained by this procedure but experience indicates that such a hazardous operation should not be attempted unless studies indicate an adequately functioning liver.

We will now consider other aspects of ascites formation. We are very much honored by having here as guests to-day several students of this topic. Dr. Harold Mankin of the Maimonides Hospital will first discuss some of the serologic factors promoting ascites.

Dr. Harold Mankin: The ascites that occurs in cirrhosis of the liver has been thought to be the result of (1) an increased capillary blood pressure in the portal tributaries and (2) a decreased albumin concentration and colloid osmotic pressure of the plasma. Of the two factors the plasma albumin concentration has been considered the more important variable conditioning the formation and resorption of ascites.

Doubt and some controversy were thrown into this simple picture by two sets of observations: (1) Dr. Ralli and her colleagues reported cases in which loss of ascites occurred without associated increase in serum albumin concentration, and focused attention upon the role of an antidiuretic substance, present in the urine of patients with ascites, absent from the urine of patients without ascites. An hormonal and renal etiology for ascites was suggested. (2) Dr. Patek and others, using concentrated human serum albumin intravenously, reported instances in which no decrease in ascites formation occurred despite elevation of the serum albumin concentration well into the normal range for long periods.

These observations have been interpreted as throwing serious doubt upon the whole concept of osmotic mechanisms in ascites. What follows is an effort to re-examine

[5] Bradley, S. E. *J. Clin. Investigation*, 25: 918, 1946.

the concept in the light of these newer developments.

It will help to focus upon the capillary-peritoneal boundary and upon the factors which might be expected to influence directly the transfer of fluid at the site where ascites is formed. In addition to (1) the capillary blood pressure and (2) the colloid osmotic pressure exerted by the plasma proteins, considered above, these include (3) the tissue pressure surrounding the capillaries, (4) the colloid osmotic pressure of the proteins of the ascitic fluid, (5) the permeability of the membrane to protein and fluid and (6) lymphatic drainage. The effective osmotic forces are not two but four in number. The net hydrostatic pressure (capillary blood pressure minus ascitic hydrostatic pressure) acting in the direction of ascites formation, is opposed by a net colloid osmotic pressure (plasma colloid osmotic pressure minus ascitic colloid osmotic pressure).

In the terms of this formulation the problem of whether or not ascites is influenced by osmotic forces is susceptible to simple experimental attack. If osmotic forces indeed operate, alteration of one or another of these pressures should affect the rate and direction of flow in a predictable manner.

Such alteration, it has been found, does influence ascites formation. Mercurial diuresis increases the albumin concentration and colloid osmotic pressure of the plasma, presumably by hemoconcentration resulting from the diuresis. The formation of ascites is decreased or reversed. Physiologic salt solution, orally administered, decreases the plasma colloid osmotic pressure. The rate of ascites formation is increased. Physiologic salt solution intraperitoneally administered decreases the ascitic colloid osmotic pressure. Ascites formation is decreased.

Certain apparently paradoxical effects are the result of the simultaneous action of opposing factors. In the cases reported by Dr. Patek elevation of the plasma albumin concentration following intravenous administration of concentrated albumin solution failed to produce the expected decrease in ascites formation. The explanation lies in the observation that diffusion of albumin from plasma to ascitic fluid was greatly increased so that the colloid osmotic pressure of the ascitic fluid rose parallel with that of the plasma and tended to counterbalance the effects of changes in the plasma.

Up to this point it has been suggested that the picture of the mechanisms in ascites must take into account the four osmotic forces operating on both sides of the capillary membrane, that alteration of these forces influences the transfer of fluid and that the permeability of the membrane to plasma proteins may modify the effects of such experimental alteration. The problem remains of the relation and relative magnitudes of the osmotic pressures.

If osmotic forces control the transfer of fluid between the plasma and ascitic fluid, it would seem plausible that during formation of ascites the net hydrostatic pressure (capillary blood pressure − ascitic hydrostatic pressure) acting toward the ascitic compartment is greater than the net colloid osmotic pressure (plasma colloid osmotic pressure − ascitic colloid osmotic pressure) which opposes it. During resorption of ascites the relation might be reversed. These assumptions are not supported by experimental measurement. The evidence suggests that the opposing osmotic forces are actually in balance, even during the formation and resorption of ascites. (1) Mercurial diuresis reverses the flow of fluid with only slight increase in the plasma colloid osmotic pressure. (2) In each patient during long periods of formation and loss of ascites and following experimental alterations the difference between the colloid osmotic pressure of the plasma (range: 200–350 mm. H_2O) and the colloid osmotic pressure of the ascitic fluid (range: 25–175 mm. H_2O) remains constant (average difference: 175 mm. $H_2O \pm 10$ per cent). It may be suggested that there exists a state of dynamic equilibrium. Osmotic equilibrium at any point in time is disturbed infinitesimally by diffusion of protein from

plasma to ascitic fluid and then restored by the passage of fluid in the same direction. Formation of ascites continues chiefly because of the continuous leakage of plasma protein into the ascitic fluid.

In this discussion we have been considering the factors acting *directly* at the site of ascites formation. One of these, the role of the lymphatics, has received no more than mention, because no evidence exists concerning alterations in magnitude of lymphatic drainage in relation to ascites. There remain a myriad of factors which may *indirectly* influence the formation of ascites. Among these are salt intake, diuresis and, of special interest, the antidiuretic hormonal factor to be discussed by Dr. Ralli. It would seem that these must act through changes in the above directly-acting forces.

The ultimate question remains unanswered: Which is the primary cause of ascites in cirrhosis? It seems likely that there is no single primary cause. Ascites is probably the result of several factors and the relative importance of each of these factors is a variable to be investigated in the individual case.

DR. HANGER: We turn now to the role of sodium chloride intake as a factor in ascites formation, a subject which has been neglected until recent years. Dr. Kunkel of the Hospital of the Rockefeller Institute will tell us of his experience in this connection.

DR. HENRY G. KUNKEL: The important role that sodium plays in the retention of fluid in patients with cardiac and renal disease has been appreciated for a number of years. However, only recently have clinicians begun to realize that a direct relationship exists between sodium intake and accumulation of ascites in patients with cirrhosis of the liver. The recent work of Whipple and co-workers on dogs rendered ascitic by constriction of the vena cava above the liver has also emphasized this relationship for ascites of purely mechanical origin.

Patients with cirrhosis of the liver and ascites show an extremely low output of sodium in the urine regardless of the sodium intake. This was first emphasized by Farnsworth and by Davidson and co-workers. In a recent study of thirteen patients at the Hospital of the Rockefeller Institute the urinary excretion of sodium chloride ranged from 0.02 to 0.13 gm. per day while the patients were on a diet containing 7 to 9 gm. of sodium chloride per day. Fecal sodium chloride excretion was only slightly higher, averaging 0.35 gm. per day. With this low excretion it is apparent that almost the entire sodium intake was used to form ascitic fluid. It was possible to demonstrate a straight line relationship between daily increments in ascitic fluid volume, as measured by intraperitoneal Evans blue, and sodium chloride intake. This relationship ended at a level of approximately 1.2 gm. sodium chloride intake per day, which appeared to be the average critical level below which ascites formation ceased. Restriction of sodium chloride in the diet of of these patients to levels below 1.2 gm. per day caused the ascitic fluid volume to remain almost stationary. In some patients no new fluid formed for periods as long as six months. In others a very slow increase in body weight and ascitic fluid volume continued although paracenteses were no longer necessary. The ascites that was present at the start of the low sodium diet remained until the patients were able to excrete increased amounts of sodium.

Studies of potassium balance indicate that, in contradistinction to sodium, patients with cirrhosis are able to excrete potassium in a normal manner. Most low-sodium diets supply very adequate amounts of potassium and there is little danger of a deficiency of this electrolyte when such diets are continued for long periods.

Excretion of water is found to rise in all patients on a low sodium diet. When no sodium is supplied in the diet for ascitic fluid accumulation, water is excreted proportional to the intake. Serum sodium levels tend to be low in patients with cirrhosis on a normal sodium intake. Long periods of sodium restriction cause only a slight fall in the serum sodium level. The body shows

an amazing ability to hold on to sodium under such conditions and preservation of the extracellular sodium level has a distinct priority over the release of sodium to form new ascitic or edema fluid. One patient who was studied actually showed a slight rise in serum sodium after five months of rigid dietary restriction of sodium. This resulted presumably from mobilization of sodium from the remaining ascitic fluid. Toxic effects from low sodium diets were encountered only in patients with renal damage or when mercurial diuretics were given along with the low sodium diet. The latter combination may cause a dangerous depletion of extracellular sodium.

The long-term clinical results of rigid sodium restriction are difficult to evaluate, just as are all other types of therapy in this disease. Certain effects, however, are clearly manifest. First, termination of ascites formation appears to be beneficial in stopping the malignant course of events brought about by removal of protein through paracenteses in the already depleted individual, thus enabling dietary therapy to become effective. Secondly, patients who remain on the low sodium diet for more than two months show a progressive rise in serum proteins. The chief limitation of this type of therapy is that long periods of treatment are necessary, a minimum of six months before real improvement appears. The problem is one of improving the general condition of the patient until he is able to excrete normal amounts of sodium in the urine and is therefore able to tolerate a higher sodium content in the diet. Not all patients regain the ability to excrete sodium and such patients may remain in a steady state for periods longer than one year. The low sodium diet aids only in partially preventing their condition from regressing. No good figures are available as yet regarding the percentage of patients who regain the ability to excrete large amounts of sodium after a prolonged period on a low sodium diet. It appears that approximately 50 per cent of patients with ascites show this effect after about six months on the restricted diet. The increased sodium excretion is accompanied by mobilization of ascitic fluid.

Another difficulty with the low sodium diet is that a few patients have trouble preserving an adequate caloric intake. This has been found only in patients who are extremely sick, particularly those with an elevated non-protein nitrogen. In the series mentioned above only one of the thirteen patients fell into this category. The general availability of low sodium protein supplements has been of considerable value in preserving an adequate protein intake. As much as 120 gm. of protein may be supplied each day to some of these patients despite restriction of salt below 1 gm.

Recently a number of short reports have appeared on the beneficial effects of the Kempner rice diet on ascites in patients with cirrhosis. These effects are probably due to the very low sodium content of this diet. In addition, it is rather remarkable that despite the very small amount of protein furnished in this diet the majority of patients show a rise in serum proteins. Such an effect is probably attributable to a combination of a fall in plasma volume and accumulation of proteins in the body that had previously been lost through paracenteses. A modification of the rice diet with the addition of various vegetables and certain of the low sodium protein foods has proven a useful method of maintaining a low sodium intake, particularly in patients followed outside of the hospital.

There is no question but that numerous factors are involved in the mechanism of ascites formation. Hypoalbuminemia and increased portal pressure represent two of the most important; also important, however, is the sodium content of the diet, since the amount of ascitic fluid formed appears to be in direct relation to the sodium intake.

DOCTOR: Would you give us more specific information as to the kind of low sodium diet you employ?

DR. KUNKEL: The diet used depended chiefly on the patient's appetite. An attempt was made to keep the total calories at 2,500

or above and also to keep protein above 50 gm. per day. In general, it appeared that the patients who were able to consume a protein intake above 100 gm. per day improved more rapidly than those who could take only 50 gm. However, this is just an impression and there are as yet no adequate studies to prove this point.

The sodium chloride content of the diet was kept as close to 1 gm. per day as possible. Analyses of such a diet showed that the intake would range between 0.8 and 1.2 gm. on different days. Certain patients who were very small, particularly the women in our series, were found to need a further reduction in sodium chloride intake before ascites ceased. These patients were carried on a diet averaging 0.8 gm. NaCl per day.

STUDENT: Do you use ordinary tap water for fluids?

DR. KUNKEL: The salt content of New York City tap water was found to be insignificant from this point of view. Analyses on two occasions several months apart showed that the tap water contained 8 mg. and 5 mg. NaCl per L., respectively.

DR. HANGER: Dr. Hilton, would you comment on Dr. Kunkel's interesting observations?

DR. JAMES G. HILTON: It is generally well known and accepted that in normal individuals under normal conditions the urinary excretion of sodium closely approximates the sodium intake even when intake values are varied from zero to large amounts. This, however, is not the case with decompensated cirrhotics accumulating ascites, as Dr. Kunkel has brought out. Mankin and Lowell found that if the salt intake of these patients was increased the rate of ascites formation and concomitant weight gain due to retained fluid was likewise increased. Dr. Kunkel has just indicated the effects of sharply reducing the sodium intake in this condition.

In a group of eleven markedly decompensated cirrhosis patients studied on the Columbia Research Service at Goldwater Memorial Hospital, every one excreted less than 5 mEq. of sodium in the urine in twenty-four hours and six excreted less than 1 mEq. on an average sodium intake of about 70 mEq./day. Addition of large amounts of sodium chloride to the diet resulted in no concomitant increase in the urinary excretion; 98 per cent of the excess sodium given was retained.

The serum sodium in patients with cirrhosis is almost uniformly depressed and in some cases is very low. In eleven patients who were decompensated, who were accumulating fluid and showed extremely low sodium excretion irrespective of intake, the serum sodium levels ranged from 121 to 138 mEq./L., averaging 127 mEq./L. These patients were further characterized by complete refractoriness to mercurials with respect to both sodium and water excretion by the kidneys. In another group of eight cirrhotic patients whose liver function tests indicated improvement and whose ascitic fluid accumulation could be controlled by moderate sodium restriction plus diuretics, the twenty-four-hour urinary sodium excretion was considerably higher than those of the previous group but still below intake except after mercurials. The serum sodium values for these individuals ranged from 134 to 138 mEq./L. Finally, in seven cirrhotic patients who were compensated and not accumulating fluid, the sodium excretion approximated intake at all times and the serum sodium ranged from 138 to 144 mEq./L.

It appears therefore that patients with severe cirrhosis who are accumulating ascitic fluid have low serum and urinary sodium levels and that this pattern reverses itself as liver compensation improves. However, it is now known that these patients have increased plasma and interstitial fluid volumes. Thus although the *concentration* of sodium in extracellular fluid may be much lower than normal, the *total amount* of extracellular fluid sodium may not be diminished.

As regards potassium we, too, in agreement with Dr. Kunkel, have found no

disturbance in the excretion or serum level of this electrolyte.

DR. HANGER: Dr. Ralli, of New York University, has pioneered in this field of mechanisms of ascites formation and I have asked her to tell us about her work dealing particularly with the role of substances with antidiuretic properties.

DR. ELAINE P. RALLI: There are many different opinions as to the factors responsible for ascites in patients with cirrhosis of the liver and, as has already been made clear, no single factor is entirely responsible. Among the earliest observations on patients with cirrhosis of the liver was the report of very low urine outputs, the twenty-four-hour urine volume sometimes being no more than 300 cc. It was noted further that once diuresis was established the rate of reaccumulation was controlled, and in the hope of initiating diuresis mercurial diuretics have therefore been given to patients with ascites.

In the patients whom we have studied it was observed that the concentration of serum albumin did not increase before the ascites was controlled but did increase when ascitic fluid did not reaccumulate.[6] An example of this is shown in Table I. In addition to this fact we have observed many patients with severe liver disease in whom the albumin was low and no ascites was present. (Table II.) Because of the observation that elevation of the serum albumin followed rather than preceded the control of ascites, and in view of the oliguria associated with cirrhosis of the liver, we began to look elsewhere for the cause of ascites and it occurred to us that the kidney might be involved. To test the role of the kidney, water tolerance tests were done in a series of patients with cirrhosis of the liver both with and without ascites. It was found that the capacity to excrete ingested water was significantly depressed in patients with liver damage, the depression being greatest in the patients with ascites. When the disease improved the water tolerance test also improved. Adlersberg and Fox[7] also reported changes in the water tolerance test in patients with liver damage. In averaging the tests that we have done on patients with and without ascites and comparing these with normals, it was found that the normal

TABLE I
EXAMPLE OF A CASE IN WHICH THE CONTROL OF ASCITES PRECEDED THE ELEVATION OF THE SERUM ALBUMIN

Months of Observation and Therapy	No. of Taps	Amt. of Abdominal Fluid Removed (L.)	Serum Proteins		
			Total Protein (gm. %)	Albumin (gm. %)	Globulin (gm. %)
1	2	24	5.7	2.2	3.5
2	2	20.9	...	...	...
3	3	32	6.1	2.3	3.8
4	2	22	...	...	...
5	1	11	6.1	2.5	3.6
6	2	27	5.7	2.5	3.2
7	2	27	6.3	2.5	3.8
8	2	22.3	...	...	...
9	2	25	4.7	2.2	2.5
10	2	20.6	5.4	2.4	3.0
11	2	21	...	...	...
12	2	15.5	5.6	2.5	3.1
13	0	0	6.4	2.8	3.6
14	0	0	6.8	2.8	4.0
15	0	0	6.2	2.4	3.8
16	0	0	6.2	2.8	3.4
17	0	0	6.2	2.8	3.4
18	0	0	7.3	3.0	4.3
19	0	0	6.3	3.0	3.3

TABLE II
EXAMPLE OF A CASE OF FATTY INFILTRATION AND CIRRHOSIS OF THE LIVER IN WHICH ASCITES WAS NEVER PRESENT AND THE SERUM ALBUMIN WAS BELOW NORMAL

Months of Observation and Therapy	Total Protein (gm. %)	Albumin (gm. %)	Globulin (gm. %)
1	5.7	1.8	3.9
2	6.1	2.8	3.3
3	6.2	3.1	3.1
4	6.7	3.3	3.4
5	6.5	3.5	3.0
6	5.7	3.2	2.5
7	5.8	3.4	2.4
8	6.0	3.4	2.6

[6] RALLI, E. P., ROBSON, J. S., CLARKE, D. and HOAGLAND, C. L. *J. Clin. Investigation*, 24: 316, 1945.

[7] ADLERSBERG, D. and FOX, C. L. JR. *Ann. Int. Med.*, 19: 642, 1943.

subject excreted 100 per cent of the ingested water in 195 minutes whereas within this period the patients with cirrhosis without ascites had excreted 82 per cent of the ingested water and the patients with ascites only 30 per cent of the ingested water. To obviate the factor of absorption from the intestinal tract, patients were given 1,000 cc. of a 5 per cent glucose solution intravenously, and again the patients with cirrhosis excreted much less than did the normal subject and again the depression was greatest when ascites was present.

In view of the known effect of the posterior pituitary hormone on urine excretion, the urines of these subjects were assayed for their antidiuretic potency and it was found that the urines of the patients with cirrhosis and ascites had a very high antidiuretic titer. You may recall that Robinson and Farr[8] reported a high antidiuretic titer in the urine of patients with evidence of nephrosis and in women with premenstrual edema. To make these assays twenty-four-hour urine samples were concentrated and dialyzed and were then assayed by the method of Burn[9] by injecting 1 cc. of the material into normal male rats hydrated to 5 per cent of their body weight. Sixteen rats in groups of four were used for each sample. Such assays have been made on the urines of a large group of cirrhotic patients. It was found that when the urine of normal subjects was injected the rats excreted 50 per cent of the ingested water within 145 minutes; when the urine of patients with cirrhosis but without ascites was injected the rats excreted 50 per cent of the ingested water in 200 minutes; when the urine of patients with ascites was injected the rats excreted 50 per cent in 360 minutes. The high antidiuretic titer found in the urine of these patients thus bore out the suggestion that the decreased urine output of patients with cirrhosis of the liver might in part be the result of increased reabsorption of water caused by increased secretion of the antidiuretic hormone of the posterior pituitary.

In continuing the studies an effort has been made to extract the antidiuretic substance from the urine and obtain it in a more purified form. This work,[10] which was initiated by Dr. George H. Stueck, Jr., in our laboratories, has been carried out by chromatographic analysis of dialyzed and concentrated urine samples. We found that the urine eluates obtained by washing columns of permutit with a solution of 5 per cent NaCl and 1 M acetic acid had a marked antidiuretic effect when injected into rats. There was no chloruretic effect with this urine eluate but we do not believe that this rules out the possibility that the substance originates in the posterior pituitary because commercial pitressin,® when treated similarly on a column of permutit and assayed in hydrated rats, also lost its chloruretic effect.

One can hypothesize therefore that the physiologic conditions associated with cirrhosis of the liver create a situation which stimulates increased secretion of the posterior pituitary hormone and that this causes a sharp reduction in urine output and retention of fluid. The fact that the retained water appears in the abdominal cavity is probably due to additional factors, namely, the increased portal pressure and the increased capillary fragility of the peritoneal capillaries. The question remains as to what factors provoke an increased secretion of the antidiuretic hormone of the posterior pituitary. The data from Verney's experiments in dogs may help in part to explain this.[11,12] Verney has shown that an increase in the NaCl concentration of the circulating blood will serve to stimulate the osmoreceptors of the supraopticohypophyseal tract and these osmoreceptors stimulate the posterior pituitary to secrete antidiuretic hormone. More data must be collected

[8] Robinson, F. H., Jr. and Farr, L. E. *Ann. Int. Med.*, 14: 42, 1940.

[9] Burn, J. H. *Quart. J. Pharm. & Pharmacol.*, 4: 17, 1931.

[10] Stueck, G. H., Jr., Leslie, S. H. and Ralli, E. P. *Endocrinology*, 44: 325, 1949.

[11] Verney, E. B. *Lancet*, 2: 739 and 781, 1946.

[12] Verney, E. B. *Brit. M. J.*, p. 119, July 17, 1948.

before this hypothesis can be accepted as applying to patients with cirrhosis of the liver but certainly some of the observations are significant: (1) the oliguria associated with the disease; (2) the fact that ascites disappears when diuresis is well established; (3) the fact that the level of serum albumin increases following the cessation of ascites and also the fact that a very low serum albumin may be present in patients who have never had ascites; finally, (4) the fact that the urine of patients with cirrhosis of the liver and ascites contains large amounts of an antidiuretic substance.

It seems unlikely that any one single factor is the cause of the ascites in cirrhosis of the liver. Rather it is the result of a series of physiologic changes in the cells and this means most of the tissue cells. These patients have loss of muscle mass, malnutrition and evidence of toxicity. It is difficult to know in what order to arrange the changes that occur in this disease and it is probable that many of the physiologic changes occur simultaneously. The fact that patients now survive repeated paracenteses and eventually cease to reaccumulate ascitic fluid is proof that restoration of the body cells and of physiologic functions can occur. Therefore, we have been prompted to consider the factors contributing to the production of ascites as mainly physiologic and as reflecting a severe alteration in the cellular constituents. The purpose of the therapy that we have used has been to stimulate restoration of tissue. Dr. Patek's report[13] on the effects of a highly nutritious diet plus dried brewers' yeast began the intensive therapy used in patients with cirrhosis of the liver. We have used very large doses of liver extract* intravenously to stimulate tissue regeneration, as liver extract is known to contain a great many growth promoting factors. Survival in many of the patients was prolonged and we were therefore able to observe patients over several years during periods of rapid reaccumulation of ascitic fluid and after ascites was controlled.[14] Punch biopsies on the livers of the patients during and after the period of ascites failed to show much change in the bands of connective tissue in the liver but the liver cells showed evidences of regeneration as the patients improved. It is reasonable to suppose that other cells in the body also were restored, and as the intracellular constituents of the cells were restored their functions also probably improved. Which factor or factors is responsible for initiating diuresis is again difficult to state but it may well be that capillary permeability is a critical factor, and that as it improves the loss of protein and other substances into the ascitic fluid is prevented and thus a more normal environment for the cells of the body is provided.

DR. HANGER: Dr. van Dyke, we would appreciate your comment on the nature of these antidiuretic substances found in the urine of patients with cirrhosis.

DR. H. B. VAN DYKE: Dr. Ralli and her associates suggest that hypersecretion of the neurohypophysial antidiuretic hormone may be an important factor in the formation of ascitic fluid in patients with cirrhosis of the liver. Their important observation to support this suggestion was the finding that "the urines of the patients with cirrhosis and ascites had a very high antidiuretic titer." This was revealed by the delayed urinary excretion of water by hydrated rats which had received injections of a substance (or substances) adsorbed from the concentrated urine by artificial zeolite (permutit). Is the substance injected derived from the patients' neurohypophysis or is the delayed excretion of water by the test rats to be attributed to other causes?

When such extracts of urine of cirrhotic patients are injected intravenously into hydrated normal dogs or dogs with diabetes insipidus, there is either no reduction in the rate of formation of urine or the reduction can be accounted for by a reduced glo-

[13] PATEK, A. J., JR. and POST, J. *J. Clin. Investigation*, 20: 481, 1941.

* Supplied by Lederle Laboratories.

[14] RALLI, E. P., LESLIE, S. H., STUECK, G. H., JR., SHORR, H. E., ROBSON, J. S., CLARKE, D. H. and LAKEN, B. *Medicine*, 28: 301, 1949.

merular filtration. Such dogs are very sensitive to neurohypophysial antidiuretic hormone, the effects of which are not associated with any important change in glomerular filtration. Therefore, it appears that some other explanation of the antidiuretic effect of urine extract in the rat must be sought. Possibly the extract directly or indirectly interferes with renal circulation thus reducing glomerular filtration and the rate of urine formation. A less likely possibility is that the injected extract causes the liberation of antidiuretic hormone from the test rats' neurohypophysis.

As has been pointed out, the pathologic physiology of the formation of ascitic fluid in the patient with hepatic cirrhosis is complex and ill understood. Dr. Ralli mentioned the derangements of metabolism and of the portal circulation which are probably important in this disease. Until more conclusive observations proving that there is hypersecretion of neurohypophysial antidiuretic hormone are reported, it appears that the search for a satisfying explanation of the factors which account for ascites in such patients must turn elsewhere.

DR. RALLI: There are one or two comments I should like to make. First, in all of the experiments that we did, controlled tests were made with saline solutions of concentrations equal to those of the antidiuretic eluate derived from urine, and in no instance did the saline solution induce as great an antidiuretic response as did the antidiuretic eluate from urine. I believe that this answers the question concerning stimulation of the animal's own pituitary. Furthermore, I would like to mention several other experiments which we have done and which have not yet been published. We have injected freshly voided urine from human subjects given injections of pitressin.® When these urines were injected into rats, an antidiuretic effect was obtained. When the same urines were injected intravenously into dogs, the antidiuretic effect was less. This may be because intraperitoneal administration evokes a greater antidiuretic response as compared to the intravenous route. To check this, we are injecting intraperitoneally into dogs the solutions that were previously given intravenously, and although enough experiments of this type have not yet been done, the evidence indicates that the route of administration, which is usually intravenous in the dog and intraperitoneal in the rat, evokes a different response.

DR. HANGER: It is obvious from the discussions of Drs. Ralli and van Dyke that the antidiuretic effects obtained with the urine of cirrhotic patients require further study as to source and underlying mechanisms.

Dr. Patek, would you give us your reactions to this whole discussion of the mechanisms operating in the production of ascites.

DR. ARTHUR J. PATEK, JR.: It is clear from the discussion that several factors are operative in the formation of ascites and that we cannot ascribe the change to disturbance of a single mechanism. For the sake of simplicity it might be useful to consider two aspects: First, a general hydrophilic tendency of the patient with liver disease. It is possible that this is due to hormonal imbalance working on a renal barrier, as Dr. Ralli suggests. This could explain in part the retention of sodium so clearly described today. Second, the localization of fluid in the abdomen due to factors that are operative at the portal vascular bed, as described by Dr. Mankin and Dr. Hanger.

Although the correlation between the level of serum albumin and the presence of ascites is fair in most cases, there are sufficient exceptions to indicate the operation of other forces. The same might be said of the antidiuretic substance: the correlation between the presence or absence of ascites and values for this substance does not always hold. Even if these correlations were excellent they would not necessarily imply a causal relationship.

The relative importance of these two aspects of the problem seems to vary somewhat in different patients. This is shown by

the fact that some patients with cirrhosis and ascites enjoy a prompt diuresis after the intravenous administration of albumin solution whereas others do not.

SUMMARY

DR. FREDERICK K. HEATH: The development of ascites in patients with cirrhosis of the liver has long been correlated with portal hypertension and hypoalbuminemia. The manner in which these and other factors may contribute to this process is considered in this clinic.

In the otherwise normal animal obstruction to the hepatic outflow (hepatic veins or vena cava) produces ascites but occlusion of the portal system results in the development of collateral circulation and hypersplenism. Portal hypertension alone, then, may furnish a larger vascular bed for diffusion and because of stasis may also tend to render this area more permeable. While both conditions are favorable to ascites formation, they do not of themselves produce it.

The role of the lymphatics has not been determined.

On this background osmotic forces operate. The net hydrostatic pressure (capillary blood pressure minus ascitic hydrostatic pressure) tending toward the formation of ascites is opposed by the net colloid pressure (plasma colloid osmotic pressure minus ascitic colloid osmotic pressure). Dr. Mankin showed that in the presence of ascites, irrespective of whether it was increasing or decreasing, the difference between the capillary and ascitic colloid osmotic pressures remains fairly constant. This state of dynamic equilibrium between opposing forces need be only slightly altered to influence the direction of fluid flow before equilibrium is regained. Thus mercurial diuresis, presumably by hemoconcentration, tends to decrease ascites. In the same fashion intravenous albumin may or may not decrease ascites depending upon how rapidly it diffuses from plasma to the ascitic compartment.

Of great interest is the finding that patients with ascites do not excrete sodium in the urine proportionally to their intake. The magnitude of this deficiency would appear to correlate with the degree of ascites and the deficiency in serum sodium levels. Ingested sodium is almost entirely diverted to the ascitic fluid which tends to increase when the daily intake of sodium chloride exceeds 1 gm. However, if salt be restricted to about 1 gm. daily, water excretion rises, serum protein values slowly increase, serum sodium concentration remains constant and no further ascitic fluid is formed. In this fashion progression of this phase of the disease may be interrupted. About one-half of Dr. Kunkel's patients maintained on low-sodium diets over a period of six months regained their ability to excrete sodium normally and concomitantly showed improvement in their ascites. Dangerous depletion of sodium has been observed on this regimen in the presence of renal damage or following the use of mercurial diuretics.

Similar to the depression in the urinary excretion of sodium, Dr. Ralli described a marked reduction in water output in cirrhotic patients with ascites. She has proposed that the renal abnormality may be due to greater tubular reabsorption of water dependent upon an increase in the posterior pituitary antidiuretic hormone and has reported finding unusual amounts of antidiuretic substances in the urine of ascitic patients. According to this evidence, the disappearance of ascites without change in hypoalbuminemia becomes understandable.

While the relative importance of these mechanisms undoubtedly varies from patient to patient and cannot be determined in advance so as to indicate a single line of therapy, they nevertheless suggest several special therapeutic approaches such as are indicated in the clinic.

Clinico-pathologic Conference

Fever, Skin Rash, Azotemia and Respiratory Failure*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, M. K. (No. 179106), was a white, married housewife, twenty-four years of age, who entered the Barnes Hospital on December 12, 1949, because of generalized swelling. The patient was too ill to relate her own history and all the information available was obtained from her husband. The family history was irrelevant. At the age of sixteen the patient had intermittent attacks of arthritis involving chiefly the wrists, ankles and right knee; all the joints were described as having been red, hot and swollen. Her past history was otherwise entirely negative. She had no other illnesses; when her only child was born four years before entry, she had an uneventful pregnancy without any evidence of complications. Seven months before entry a blotchy, purplish non-confluent skin eruption appeared on the patient's face; the lesion was neither vesicular nor pustular. It was particularly prominent over the forehead and cheeks; there was no other skin involvement. A few days after the skin rash developed the patient also had the onset of fever, nausea, vomiting and weakness. She remained in bed for several months. The eruption disappeared five weeks after it began. One month after she became ambulant again the patient's feet became so painful that she was unable to walk. No other evidence of acute inflammation was obvious. About the same time several teeth were extracted. Soon thereafter she developed marked anorexia and her weight fell rapidly from 119 to 80 pounds. Her legs swelled progressively. Three months before admission she entered another hospital where many procedures, including a sternal marrow aspiration, were performed. The patient remained in the hospital for three or four weeks. During this period her abdomen became enlarged. No diagnosis was made and the patient was not given any specific treatment. Three weeks before admission she became so weak that she was forced to remain in bed all of the time. She complained of difficulty in breathing, inflammation of the eyes and pain in the left ear.

Physical examination at the time of entry revealed the temperature to be 38°c., pulse 160, respirations 45 and blood pressure 110/70. The patient was extremely ill. Her face was swollen. There was such a striking degree of anasarca that pitting edema could be demonstrated anywhere over the entire surface of the body. The respirations were rapid but the patient was not cyanotic. Many ulcers in the process of healing were noted over the arms and legs. Examination of the eyes revealed that the pupils reacted well to light and accommodation. The fundi showed slight tortuosity of the retinal vessels but no hemorrhages or exudates. The discs appeared normal. The left ear drum was suggestively bulging. Purulent exudate was present in both nares and there were small ulcerations in the buccal mucosa. There was questionable induration

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over the left side of the neck where the skin was red. Examination of the lungs revealed signs of consolidation over the left upper lobe. A few moist rales were heard in this area. There also were signs of a pleural effusion over the lower third of the left chest. Examination of the heart revealed the sounds to be distant but otherwise not abnormal. There were no murmurs, the rhythm was regular and no friction rub was audible. The abdomen was tremendously distended and signs of fluid were obvious. There was diffuse tenderness on palpation but no organs or masses could be detected. The remainder of the examination was not remarkable.

Laboratory data were as follows: Blood count: red cells, 4,620,000; hemoglobin, 12.5 gm. per cent; white cells, 6,100; differential count: myelocytes, 1 per cent; metamyelocytes, 5 per cent; band forms, 29 per cent; segmented forms, 50 per cent; lymphocytes, 13 per cent; monocytes, 3 per cent. Urinalysis: specific gravity, q.n.s.; protein, 4+; sugar, negative; sediment, many hyaline and finely granular casts; rare red cells; a few white cells per high power field. Fat globules and "sulfa crystals" were also reported. Venous pressure: 150 mm. of saline. Circulation time (decholin); 11 seconds. Blood chemistry: non-protein nitrogen, 80 mg. per cent; total protein, 3.9 gm. per cent; albumin, 1.3 gm. per cent; globulin, 2.6 gm. per cent; carbon dioxide combining power, 16.2 mEq./L.; chlorides, 120 mEq./L.; cephalin-cholesterol flocculation test, 4+; thymol turbidity test; 21 units. Blood cultures: Staphylococcus albus and hemolytic gram-positive cocci in chains. Culture of pus from ear: Staphylococcus albus. Electrocardiogram: very low voltage and supraventricular tachycardia.

On admission the patient was begun on a regimen which included 50,000 units of penicillin immediately and 200,000 units every two hours thereafter. She also received 0.5 mg. of streptomycin every six hours. She was seen by an otolaryngologist who noted the epiglottis to be injected, slightly swollen and deviated somewhat to the right; the cords, however, were normal. The left ear drum was described as red and bulging. Two hours later edema of the epiglottis had increased, causing approximately 50 per cent obstruction of the airway. The cords could no longer be seen. Because of this progression in edema it was decided to perform a tracheotomy. During the course of the tracheotomy the patient developed marked cyanosis and stopped breathing. A satisfactory airway was obtained through the tracheotomy and artificial respiration was instituted, but despite these and other emergency measures the patient died.

CLINICAL DISCUSSION *

DR. CARL V. MOORE: This woman was admitted on a Sunday afternoon and although she lived only a few hours considerable information was obtained. There are other data which would be helpful but because of the brief hospital course these are unavailable. When she was admitted she was so ill that she could not give a satisfactory history. Further, her husband was almost hysterical and not able to offer as much information as would have been desirable. At the outset, therefore, we must remember that the historical information must be considered as probably lacking accuracy. I should like to ask Dr. Lieberman, who was on the laboratory service when this patient entered the hospital, to comment on the blood culture results. Dr. Carl Harford told me shortly before this conference began that he was not entirely sure about the reliability of these reports.

DR. DAVID M. LIEBERMAN: The patient's veins were collapsed and very difficult to find; in order to obtain blood for culture her arms were first wrapped in warm packs. Four attempts were made before 20 cc. of blood were finally obtained, and none of us felt confident that the blood had been obtained aseptically.

* It should be noted that this clinico-pathologic conference differs from those usually published in the Journal in that the discussion was carried on by students selected from the Senior class rather than by members of the faculty.

DR. MOORE: No one was able to obtain a history that this patient had taken sulfonamides. The result of the urinalysis, however, indicates that sulfonamide crystals were found in the sediment. Mr. Meyer, I believe that you were on the ward at the time and examined the patient's urine. Would you tell us about this finding?

MR. WALTER L. MEYER: I saw "wheat-sheaves" which appeared to me to be characteristic sulfonamide crystals. I could think of no other crystal which these could have represented.

DR. MOORE: If indeed this patient had taken sulfonamides, that fact might well have been important to our considerations; we shall have to accept this urinary finding as evidence of sulfonamide intake. It seems quite clear that this patient had an infection. Whether the bacteremia was real or whether the results were due to contaminants is not clear. It is also of interest that at the age of sixteen she had had migratory polyarthritis and several months before entering the hospital she had some teeth extracted. Can you relate all of these facts, Mrs. Rodgers?

MRS. DOROTHY L. RODGERS: They can be related although they are not necessarily so. It cannot be stated with certainty that the attack of migratory polyarthritis at sixteen was an attack of rheumatic fever but it certainly is suggestive of that diagnosis. Dental extraction is frequently followed by transient bacteremia and patients who have rheumatic valvular disease are predisposed to develop subacute bacterial endocarditis as a result of such bacteremia. Therefore, subacute bacterial endocarditis must be considered. There is other evidence that the patient had an upper respiratory infection with otitis, possibly cellulitis of the neck, probably laryngitis and almost certainly pneumonia. Staphylococcus albus was recovered from the discharge from the ear, but one can certainly not be very sure that the pneumonia was due to Staphylococcus albus.

DR. MOORE: Are you hesitant about ruling out the diagnosis of subacute bacterial endocarditis engrafted on a rheumatic valve?

MRS. RODGERS: I do not believe it can be entirely ruled out although the patient had no murmurs. Certainly, the absence of murmurs is strongly against the diagnosis but proven cases have been reported in which no murmurs were heard.

DR. MOORE: Are you in agreement with that statement, Mr. Hurst?

MR. PETER L. HURST: I believe that the likelihood of acute bacterial endocarditis is very small, particularly in view of the course, the blood picture, the other obvious pyogenic infection and as a matter of fact, the entire clinical picture. I can think of another disease which is so much more likely that I would hardly consider bacterial endocarditis.

DR. MOORE: Will anyone support the diagnosis of subacute bacterial endocarditis, or shall we stop this from further consideration?

MR. WILLIAM M. HEBERT: I hesitate to support it, Dr. Moore, but I likewise do not believe it can be completely disregarded as a possibility.

MR. MELVIN H. BECKER: Is it possible that the patient had acute bacterial endocarditis?

DR. MOORE: I think that suggestion deserves consideration since acute bacterial endocarditis may be a complication of pyogenic infections such as pneumonia, otitis, etc. This patient's anasarca was certainly very striking. We know that her plasma proteins were low, that she was azotemic and that she had proteinuria. What interpretation do you place on this group of findings, Mr. Iwano?

MR. JOSEPH H. IWANO: The edema could be explained on the basis of the low plasma proteins. If one calculates the osmotic pressure exerted by the albumin and globulin fractions in this patient's serum, one obtains a value far below that usually taken as the critical level.

DR. MOORE: I agree that the calculated value is very low and could explain the occurrence of edema. Do you believe that

we can eliminate the factor of cardiac decompensation as contributing to the development of anasarca?

MR. IWANO: Neither her circulation time nor her venous pressure were abnormal. There were no murmurs. I would be willing to rule out cardiac failure.

DR. MOORE: If the edema were due to low plasma proteins, and if there were no cardiac element in the anasarca, Mr. Hastings, how would you explain the hypoproteinemia?

MR. CHARLES M. HASTINGS: The patient certainly had serious renal disease which could have explained the loss of protein.

MR. FRANK A. HOWARD: In regard to mechanisms of anasarca, it is worth noting that there are factors other than the low plasma protein which may have been involved. It has been shown experimentally that when serum protein values are returned to normal and the blood volume is doubled, anasarca is still maintained. In other words, there is a defect in the manner in which the kidney handles water.

DR. MOORE: In other words, there is salt retention.

MR. HOWARD: Yes, there is sodium retention and also a disturbance in water reabsorption. The mechanism has not been entirely explained.

DR. MOORE: In line with this discussion I think there is a blood chemical value that must be puzzling all of us, namely, the chloride value of 120 mEq./L. Do you have an explanation for that, Mr. Howard?

MR. HOWARD: It is said that in the nephrotic syndrome chlorides are handled poorly. The chlorides may be reabsorbed more rapidly than normal and may result therefore in a high serum chloride level. Other factors also may be operative; for example, the hemoconcentration.

MR. MAURI FELDAKER: In sulfonamide nephrosis there may be retention of chlorides. If this patient really had sulfonamides, perhaps that is also a factor in this case.

DR. MOORE: Does edema appear in sulfonamide nephrosis?

MR. FELDAKER: It may.

DR. MOORE: Before we discuss further the specific nature of the patient's renal disease, I should like to ask for an explanation of the 4+ cephalin-cholesterol flocculation and the thymol turbidity of 21. Do those findings mean that the patient had hepatic insufficiency?

MRS. HARRIET L. LIVINGSTON: The cephalin-cholesterol flocculation test may be positive either with a relatively high serum globulin or a relatively low serum albumin. The fact that this patient had a low albumin and a high globulin may constitute therefore the explanation of the positive cephalin-cholesterol flocculation. The thymol turbidity test is also positive in patients with nephrosis, presumably on the basis of lipemia; since it seems likely that this patient had nephrosis, that mechanism may well have obtained here.

DR. MOORE: Is it not true that there is another factor besides elevated blood lipid which is necessary for a positive thymol turbidity test?

MRS. LIVINGSTON: It is said that turbidity results from a combination of thymol, globulin and lipid; probably this patient had an abnormal globulin in her serum.

DR. MOORE: I believe that elevation in the beta globulin contributes to a positive thymol turbidity test. The explanations which you offer for the abnormal liver function tests are quite tenable, but are you willing to eliminate completely the possibility of hepatic disease *per se?*

MR. THOMAS A. BURCHAM, JR.: It is pertinent to point out that patients with the nephrotic syndrome show not only a quantitative change but also qualitative changes in their serum proteins as shown by electrophoretic studies; these changes particularly involve the albumin fraction. Such changes might well explain the results of the liver function tests.

DR. MOORE: You would therefore not be inclined to consider the abnormal liver function tests as manifestations of hepatic disease.

MR. HEBERT: Bradley points out that our usual methods of determining albumin

and globulins are grossly inaccurate. When one studies protein fractions by more sensitive methods such as electrophoresis, he finds that there is more globulin in the albumin fraction than is reported by usual laboratory procedures. Thus the value for serum globulin may actually be higher and that for serum albumin lower than reported by routine laboratory tests.

DR. MOORE: In this patient then the albumin may have been less than even 1.3 gm. per cent.

MR. HEBERT: Very possibly.

MR. HASTINGS: This patient had pneumonia and with pneumonia there is frequently associated anoxemia. Conceivably anoxemia might play a part in hepatic damage and give rise to abnormal liver function tests.

DR. MOORE: Furthermore, she had evidence of infection in her middle ear, and infection *per se* may be manifested by abnormal liver function studies. I would agree that one cannot be certain whether or not the patient had hepatic disease. Mr. Streeter, what about the changes in the mucous membranes and in the skin? Were they manifestations of the terminal infection or can they be related to the skin changes which were noted at the beginning of the patient's illness?

MR. RALPH T. STREETER: The skin changes which the patient had early in her course certainly suggest disseminated lupus. Some of the later skin lesions, particularly those of the mucous membranes, may have arisen on that basis also.

MR. HEBERT: In spite of my earlier failure to champion the cause of subacute bacterial endocarditis, I should like to mention that Libman in 1913 described a series of cases of subacute bacterial endocarditis which he followed for some years and described as "healing." Nine such cases terminated with uremia and some of the patients exhibited a peculiar brownish discoloration on their faces.

DR. MOORE: Did any of those patients have generalized anasarca?

MR. HEBERT: No, I do not believe so.

DR. MOORE: We will not dismiss the possibility of subacute bacterial endocarditis completely. Mr. Meyer, do you wish to support Mr. Feldaker's suggestion of sulfonamide nephrosis?

MR. MEYER: I think it must be considered as a terminal episode; but I believe that if the patient had been treated with sulfonamides over a long period of time, the history would have been clear on that point.

DR. MOORE: Mr. Becker, are there other forms of nephrosis which should be considered? Might this patient have had either primary lipoid nephrosis or the nephrotic stage of glomerulonephritis?

MR. BECKER: Neither can be ruled out. The clinical findings were characteristic of the nephrotic syndrome, but what the pathologic lesion will be I am unable to say.

DR. MOORE: Does the absence of an elevated blood pressure help in reaching a diagnosis?

MR. BECKER: It is said in the protocol that the patient's retinal vessels showed some tortuosity. That finding may have indicated that she once had hypertension.

DR. MOORE: Did the report from the hospital in which the patient had been earlier indicate that she had had hypertension previously?

DR. CHARLTON DE SAUSSURE: No mention was made in the report of the patient's blood pressure.

DR. MOORE: Mr. Hurst, you stated earlier that you could think of a much more likely diagnosis than any we have been considering. I am sure all of you have been "straining at the bit" to discuss it.

MR. HURST: I agree with Streeter that the patient had disseminated lupus erythematosus.

DR. MOORE: Are there any dissenters?

MR. BECKER: In support of the diagnosis it should be mentioned that a nephrotic-like syndrome has been described in disseminated lupus.

MR. HEBERT: "Wire-loop" lesions are a common finding in lupus erythematosus; and if Bradley is correct in his interpretation

of the pathogenesis of nephrosis, one can even explain the fat globules which were seen in this patient's urine. Bradley postulates that the primary lesion is in the glomeruli and that protein is excreted through them. The tubules are relatively normal and reabsorb protein. In so doing they become damaged. Lipid is deposited in these cells from the blood and when they desquamate lipid-laden cells and free lipid are found in the urine.

DR. MOORE: Are there other comments in regard to the hyperchloremia?

MRS. RODGERS: Recently, Dr. Wood correctly made a diagnosis of acute hemorrhagic pancreatitis on the basis of a high serum chloride. In lupus erythematosus it is reported that perihepatitis, perisplenitis and peritonitis may occur. Perhaps peripancreatitis also develops and could explain the increase in serum chloride.

DR. MOORE: Would peripancreatitis do so or would there not have to be a lesion in the pancreas itself?

MRS. RODGERS: Probably the lesion would have to be in the pancreas.

MR. HEBERT: Since we are postulating that the patient had lupus erythematosus which is primarily a disease of the reticuloendothelial system, it is possible that vascular lesions in the pancreas may occur.

MRS. LIVINGSTON: There have been cases of lupus erythematosus with acute hemorrhagic pancreatitis noted at autopsy.

DR. MOORE: Would you care to make a definite diagnosis of both disseminated lupus and of acute hemorrhagic pancreatitis?

MRS. LIVINGSTON: No, I would be loathe to do so since the hyperchloremia could be explained on the basis of a renal lesion alone.

DR. MOORE: Would you comment on the electrocardiographic changes, Mr. Burcham?

MR. BURCHAM: The voltage was extremely low and there was a supraventricular tachycardia. I believe Dr. Massie says that those changes are not in themselves sufficient to make a specific cardiac diagnosis.

MR. FELDAKER: Capps points out that abdominal distention which results in elevation of the diaphragm and a more horizontal position of the heart may give rise to low voltage.

DR. MOORE: Low voltage also occurs with pericardial effusion. This patient had fluid in her peritoneum and fluid in her left chest. Is it possible that she also had a pericardial effusion?

MR. STREETER: I think it is likely. Pericardial effusion is not uncommon in lupus erythematosus and, when it occurs, low voltage in the electrocardiogram is a consistent finding.

DR. MOORE: On the other hand, the pulse pressure was 40. Does that disturb you?

MR. STREETER: I would have expected a much smaller pulse pressure if there had been a pericardial effusion.

MR. BURCHAM: Much evidence for a diagnosis of lupus is available, but many of the findings are subject to interpretation. I think it is conceivable that this patient had nephrosis and not lupus.

MR. HOWARD: The term, nephrosis, is a rather loose one which may apply to a number of clinical pictures. It may represent a stage of chronic glomerulonephritis, it may be seen in lupus erythematosus and, according to many clinicians, it may be an entity unto itself, so-called lipoid nephrosis. I certainly think that in this situation lupus erythematosus is the most likely diagnosis.

DR. MOORE: If, Mr. Burcham, you make a diagnosis of nephrosis, the arthralgia which the patient had at the age of sixteen would have to be considered an unrelated disease, would it not?

MR. BURCHAM: Yes.

MR. HOWARD: Most patients recover from lipoid nephrosis whereas when nephrosis is a manifestation of lupus erythematosus recovery is unlikely.

MR. HURST: I was going to make a similar point. The fact that this patient died in uremia speaks strongly against the diagnosis of lipoid nephrosis.

MR. STREETER: Did she die of uremia or of respiratory failure?

MR. BURCHAM: She certainly could have died of the infection.

DR. MOORE: Mr. Hurst, do you believe the patient will have verrucous endocarditis or acute bacterial endocarditis?

MR. HURST: There is no way to know. Many patients with verrucous endocarditis have no clinical signs of it. Whether or not we can make a diagnosis of acute bacterial endocarditis depends on our interpretation of the blood culture findings. If the blood culture was indeed positive, it would lend much weight to a diagnosis of acute bacterial endocarditis.

MR. BECKER: It is stated in the literature and in the pathology textbooks that about 50 per cent of patients with lupus erythematosus have verrucous endocarditis of the Libman-Sacks type. This patient would therefore have a good chance of having verrucous endocarditis if she had lupus.

MR. IWANO: In retrospect the leukopenia would be consistent with the diagnosis of lupus erythematosus also.

MR. MEYER: Several days ago I reviewed the blood films which were made on this patient when she was in the hospital, and I thought I found several lupus erythematosus cells.

DR. MOORE: I assume most of you agree that this patient probably had lupus erythematosus and you will not be surprised if Dr. Dammin shows us pathologic findings consistent with that diagnosis. Dr. de Saussure, what was the house staff diagnosis?

DR. DE SAUSSURE: Disseminated lupus erythematosus.

Clinical Diagnosis: Disseminated lupus erythematosus.

PATHOLOGIC DISCUSSION

DR. MARGARET CARTER: In addition to generalized anasarca, the face, eyelids and neck were markedly swollen. The subcutaneous tissues of the neck were indurated and hyperemic. The epiglottis, vocal cords and the mucosa of the trachea were dusky pink and edematous. Bilateral hydrothorax was present with 1,400 cc. of pale fluid in the left pleural cavity and 500 cc. in the right. The left lung was small, compressed, purple and airless, and the right lung was dark red and subcrepitant throughout. The heart was normal except for two verrucous nodules on the atrial surface of the mitral valve, 4 and 6 mm. from the margin of closure. The larger verrucus was sessile, 4 mm. in diameter, irregular, yellow and firm. The other was 2 mm. in diameter and was attached to the valve by a short, thin pedicle. The bases of the valves were normal.

There were 9,000 cc. of slightly cloudy pale fluid in the abdominal cavity. On the left wall of the pelvis in the cul-de-sac of Douglas there was a sharply localized zone of acute fibrinous peritonitis. The kidneys were normal in size. Their external surfaces were smooth and pale yellow with mottled red markings. The cut surface of the cortex bulged slightly and was predominately yellow with the architectural markings less distinct than usual. The soft, tan retroperitoneal lymph nodes were slightly enlarged. The spleen weighed 180 gm. and contained two large infarcts. One at the lower pole was yellow, firm and wedge-shaped; the other at the upper pole was circular, soft and partially fluid. The liver, pancreas and other organs were not remarkable.

DR. GUSTAVE J. DAMMIN: When we initially reviewed the anatomic lesions of this case they suggested that the patient might have had nephrosis, probably of the mixed variety, with albuminuria, a low total serum protein with reversed albumin-globulin ratio and the terminal acquisition of local peritonitis and of cellulitis of the subcutaneous tissue of the neck, larynx and trachea. The anasarca and the fluid in the serous cavities were other evidences of low serum proteins. The kidneys were normal in size; the cortices were unusually pale yellow and in the tubules there were large amounts of doubly refractile fat, as illustrated in Figure 1. Some of the fat was in the epithelium and other parts of it in the interstitial tissues. Considerably more fat

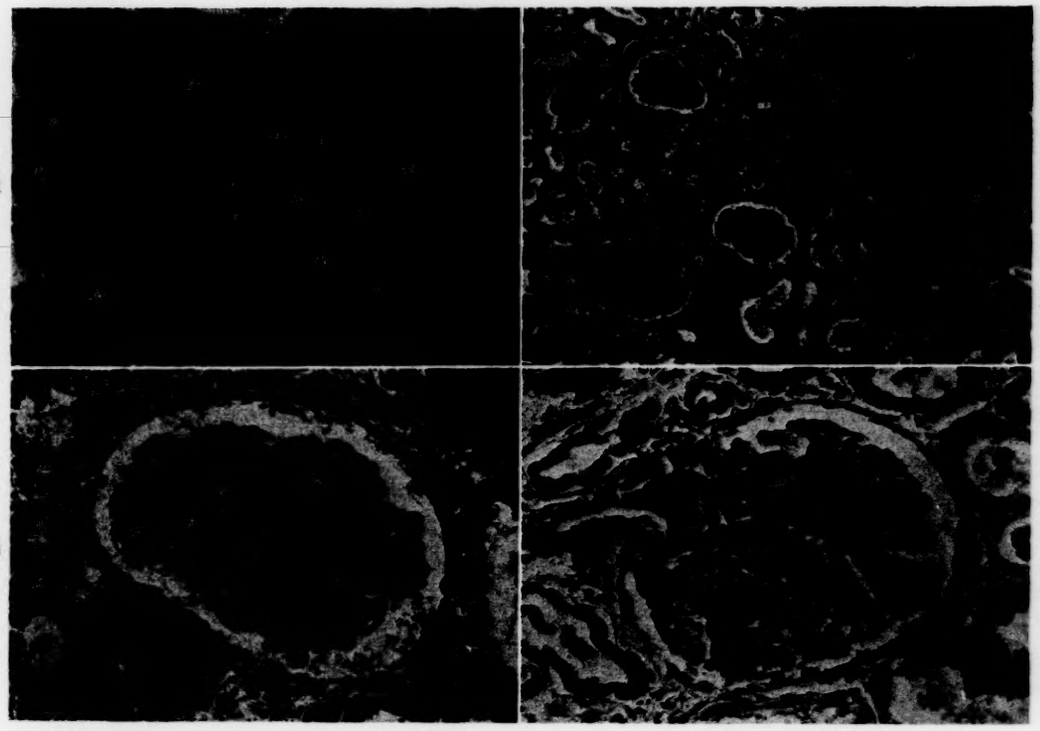

FIG. 1. Crystals of doubly refractile lipoid in the tubules and interstitial tissue of the kidney as demonstrated under polarized light.
FIG. 2. Glomeruli with thickened capillary basement membranes and tubules with hyaline granular degeneration of the epithelium in a general view of the kidney.
FIG. 3. Detailed view of the "wire loop" lesion in the glomeruli of the kidney.
FIG. 4. A necrotic tuft in a glomerulus. This lesion is compatible with but not specific for lupus erythematosus.

was stained by Sudan IV than was indicated by examination under polarized light. All of these findings were consistent with a diagnosis of nephrosis, probably of the mixed variety in view of the elevated nonprotein nitrogen terminally.

Examination of permanent sections of the kidney such as that illustrated in Figure 2, however, reveals evidence of granular degeneration in many tubules but none of the usual changes of chronic glomerulonephritis. In the glomeruli there is thickening of the basement membrane, a finding which introduces the differential diagnosis of disseminated lupus erythematosus. The prominent thickening of the basement membrane in this case is more clearly represented in Figure 3 and is of such a pronounced degree as to be more suggestive of the "wire loops" of lupus erythematosus than of the glomerular lesion of lipoid nephrosis. At this point there were some members of the Department of Pathology who were dissatisfied with the immediate impression of lipoid nephrosis. Dr. Thomas Young and Dr. Seth Barnes took the specimen of serum which had been obtained at autopsy and incubated it for twenty minutes with normal leukocytes in an attempt to produce lupus erythematosus cells. Several examples of the typical large basophilic inclusions in what are probably polymorphonuclear leukocytes with displaced, distorted, peripheral nuclei were found in films they prepared from that mixture. This finding certainly stimulated further study of the sections, especially of the kidneys and the heart, in order to identify other lesions of lupus erythematosus.

In distinguishing the thickening of the glomerular basement membrane that occurs in lupus erythematosus from that which occurs with lipoid nephrosis one must depend on qualitative differences which

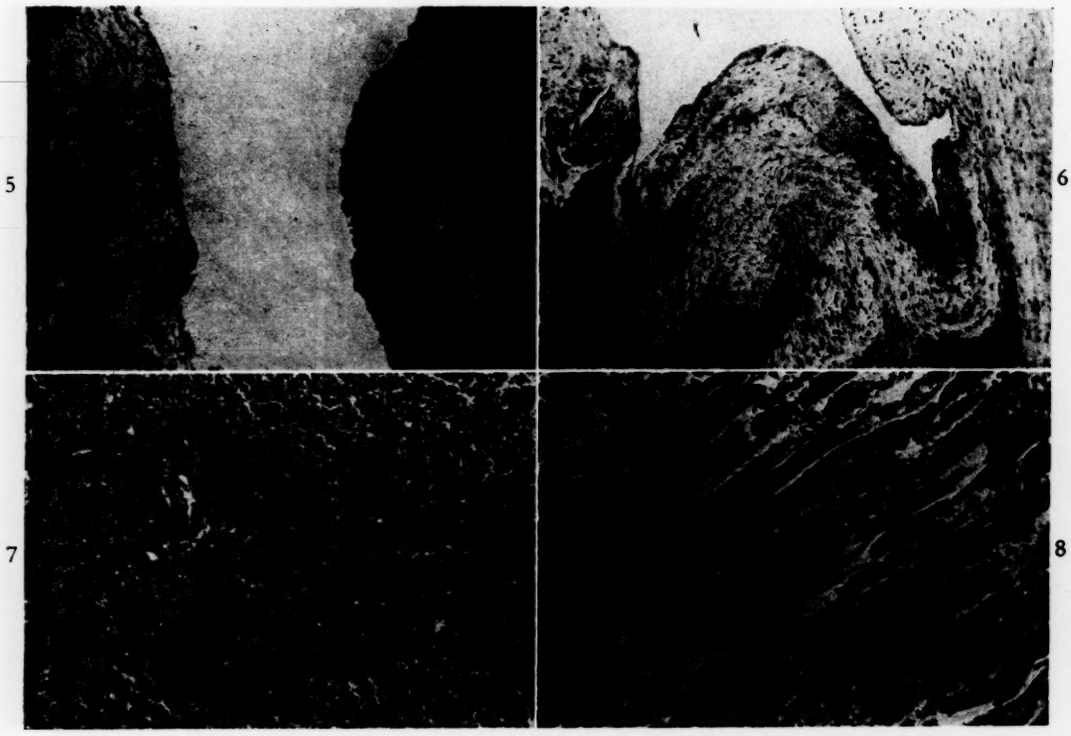

FIG. 5. A necrotic verrucus of atypical endocarditis on the mitral valve and a cellular portion of the valve adjacent to the base of the lesion.
FIG. 6. Verrucus of atypical endocarditis with an outer layer of intact endothelium, a layer of fibrinoid necrosis of collagen and a base of proliferated fibroblasts.
FIG. 7. Thickened collagenous collars about arterioles in the spleen, suggestive but not diagnostic of lupus erythematosus.
FIG. 8. Muscle and interstitial tissue from the neck with a severe cellulitis in which many gram-positive cocci were identified.

are more apparent in sections stained differentially. The basement membrane in lipoid nephrosis, arteriolar disease, and related diseases consists entirely of thickened collagen. The resulting membrane is eosinophilic but only slightly so. In lupus the membrane is remarkably eosinophilic—actually a manifestation of fibrinoid change in the collagen. With Heidenhain's aniline blue stain the membrane does not give the reaction of collagen; instead of staining blue it stains reddish or reddish purple, and with Masson's trichrome stain it is brownish or brownish red instead of green. The thickened glomerular basement membranes in this case stained in the non-specific manner of the lesions of lupus with these stains. After further search of the kidneys for other evidences of lupus, we found in one glomerulus a necrotic tuft (Fig. 4), but we were not able to find any examples of the hematoxylin bodies that have been described by Klemperer.*

The verrucous lesions on the mitral valve were originally interpreted by those defending the diagnosis of lipoid nephrosis as non-bacterial thrombotic endocarditis. In the microscopic sections, however, there were certain points which enabled us to distinguish the typical verruca of lupus erythematosus from those of non-bacterial endocarditis or the verruca of rheumatic endocarditis. Figure 5 shows a portion of the valve leaflet on one side and the edge of a vegetation on the other. This part of the vegetation does not show the intact endothelium over the substance of the vegetation; it was present in many other parts of

* KLEMPERER, P. Pathogenesis of lupus erythematosus and allied conditions. *Ann. Int. Med.*, 28: 1–11, 1948; KLEMPERER P., POLLACK, A. D. and BAEHR, G. Pathology of disseminated lupus erythematosus. *Arch. Path.*, 32: 569–631, 1941.

the vegetation and constitutes a diagnostic feature of the valvular lesions in atypical endocarditis. Most of the vegetation is made up of strikingly eosinophilic, necrotic, fibrinoid substance. In Figure 6 there is a more general view of the vegetation showing the intact endothelium and immediately beneath it a broad band of fibrinoid degeneration of collagen. The marked cellularity of the base of the lesion apparent in both these illustrations is due to proliferation of fibroblasts. The extensive necrosis makes the diagnosis of rheumatic fever unlikely. On the other hand, marked cellularity of the base, although inconsistent with a nonbacterial type of valvulitis, is compatible with rheumatic fever. It has been pointed out frequently by Gross and a number of others that the rheumatic process prevails in the base of the valve and the valvular ring and usually involves the entire substance of the valve to the point at which the verrucus occurs. In this case there was no involvement of the valvular ring nor was there any inflammatory reaction in that portion of the valve between the vegetation and the base of the valve. No bacteria were found in the vegetation, nor were Aschoff bodies found in the myocardium.

In the spleen we looked for the change in the collagen around the splenic arterioles and in Figure 7 there is illustrated the slight increase of collagen that was present; it was not of a degree we would consider helpful in establishing the diagnosis of lupus. Figure 8 is of a section of the tissue from the neck showing the marked cellulitis; bacterial stains showed numerous gram-positive cocci throughout the section.

In the final analysis, although we found no other striking evidence of disseminated lupus erythematosus, on the basis of the lesions in the kidney and in the heart we made that diagnosis. Fat in the renal tubules, demonstrated here both by staining and double refraction, has been described in disseminated lupus. We also accept the positive cephalin-cholesterol flocculation and thymol turbidity tests as evidence of lupus because we found no parenchymatous lesions in the liver to explain them. Positive flocculation tests have been reported in lupus accompanied by complicating bacterial infection, a situation which obtained in this case.

Anatomic Diagnoses: Disseminated lupus erythematosus involving the kidneys ("wire loop" lesion) and heart (atypical verrucous endocarditis); anasarca; localized fibrinous peritonitis involving the left wall of the pelvis; cellulitis of the neck involving the skin, muscles, thyroid, trachea and larynx.

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Case Reports

Postarsenical Obstructive Jaundice Complicated by Xanthomatosis and Diabetes Mellitus*

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THE jaundice which may follow the administration of arsenical preparations may be either of the hepatocellular variety or of the intrahepatic obstructive type.[1] The cases of postarsphenamine jaundice in which the obstructive manifestations predominate were first set aside as a group by Hanger and Gutman in 1940.[2] Since that time a number of cases of postarsenical jaundice of the obstructive type have been reported.[7–13] In two, xanthomatosis was a complicating feature.[10,19]

CASE REPORT

The patient, S. M., a fifty-four year old West Indian-born, colored merchant seaman was transferred to Goldwater Memorial Hospital on November 5, 1948, with the diagnoses of arsenical hepatitis and benign xanthomas.

His history dates back to the age of twenty-five when he developed a purulent urethral discharge and a penile sore for which he received no treatment. He was asymptomatic until the Spring of 1947 when, on a routine checkup, it was noted that the patient had a positive Wassermann test. At that time he received four injections of a bismuth preparation without reaction. Treatment was voluntarily discontinued until July, 1947, when repeated Wassermann tests were first positive and then negative. He was given ten weekly injections of bismuth and in December, 1947, he was started on intravenous arsenicals. Following the first injection he felt weak and feverish. A second injection was given one week later and the patient noted a somewhat more severe reaction with fever, anorexia and muscle and joint pain. A third injection was given one week after the second and again the patient noted a similar reaction. The fourth and final arsenical injection was given three weeks after the first and immediately following it, the patient noted that his urine was dark and his stools clay-colored. He felt weak and feverish and was plagued with an intense generalized pruritus. The next day he returned to the clinic where it was observed that he was jaundiced and that his liver was enlarged. He gave no history of antecedent jaundice and had never been told he had liver disease.

On December 16, 1947, he was hospitalized elsewhere. It was noted that the patient was feverish, jaundiced and anorexic. His temperature was 103°F., pulse 100/minute, blood pressure 126/76. The heart and lungs were normal. The liver was palpated 3 cm. below the costal margin. There was no shifting dullness or fluid wave. The cephalin-flocculation test was 4+ initially, but returned to normal in three months. (Table I.) His alkaline phosphatase was 22.1 King-Armstrong units and his icterus index 102. Bile was present in the urine and urobilinogen was present in a 1:20 dilution. His total cholesterol level was 640 mg. per cent with 122 mg. per cent as esters. The albumin/globulin ratio was 3.9/3.3. Gradually his alkaline phosphatase level rose. Urobilinogen disappeared from the urine. His icterus and high cholesterol levels persisted. Because of the marked degree of obstructive jaundice without pain it was deemed advisable to rule out a neoplasm. The patient was explored on February 16, 1948. At operation the gallbladder was small and the pancreas was normal. The liver was enlarged, smooth and had a dark greenish-blue hue. A

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probe was passed with ease through the open common bile duct into the duodenum. The common duct was dry. Two small lymph nodes were found at the point where the cystic artery crosses the cystic duct and these were removed. Postoperatively the patient continued to receive

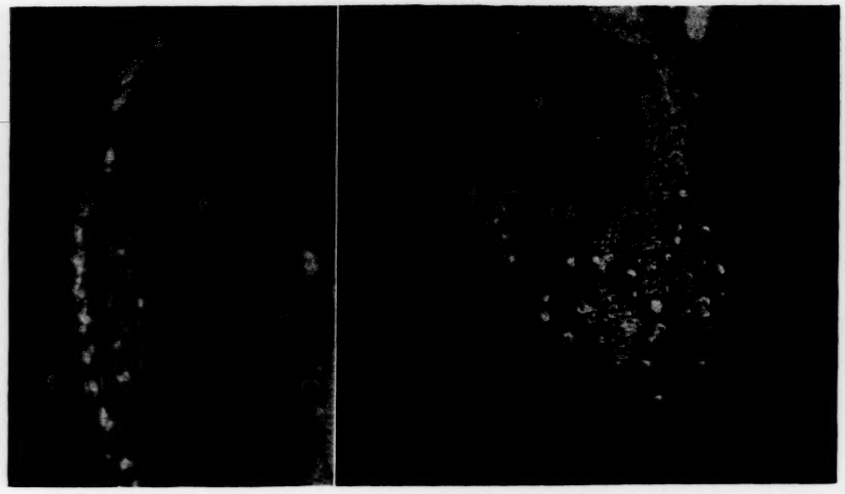
was constantly bothered with an intense pruritus. His stools gradually became darker and his urine lighter.

Ten months after the onset of jaundice he noticed the appearance of many painful, firm nodules on his elbows, knees and ears. These

TABLE I

Date	Icterus Index	Bilirubin		Albumin/ Globulin (gm. %)	Cephalin-Flocculation Test	Thymol Turbidity (units)	Alkaline Phosphatase (K.A. units)	Cholesterol		Urine		Fasting Blood Sugar (mg. %)
		Total (mg. %)	Direct (mg. %)					Total (mg. %)	Esters (mg. %)	Bile	Urobilinogen	
1/5/48	102	....	...	3.9/3.3	4+	...	....	640	122			
1/19/48	71	....	...	.....	.....	...	....	937	426	Positive	1/20	
1/29/48	95	....	...	.....	2+	...	22.1	795	199	Positive	1/10	
2/26/48	102	....	...	.....	.....	...	....	960	506	Positive	Neg.	
3/22/48	70	....	...	.....	Negative	...	....	576	86			
3/29/48	71	....	...	4.9/3.4	Negative	...	30.7	925	293	Positive	Neg.	
7/1/48	55	....	...	4.1/2.3	Negative	...	86.3	....	...	Positive	1/10	
9/13/48	50	....	...	3.7/2.2	Negative	...	27.8	....	...	Positive	1/10	
10/11/48	40	....	...	.....	.....	...	17.9	....	...	Positive	1/10	
Goldwater Memorial Hospital												
11/15/48	...	....	...	3.4/4.7	Negative	...	65.2	1800	...	.....	Increased above normal	250
11/17/48	...	....	...	.....	.....	...	....	....	...	Positive		394
11/18/48	125	10.5	4.1	2.8/3.6	Negative	...	56.3	1875	353	.....		250
11/29/48	...	....	...	.....	.....	...	....	1953	890	.....		
12/3/48	50	6.9	3.8	.....	.....	...	....	....	...	Positive		
12/8/48	...	....	...	.....	.....	4.3	....	1118	397	Positive		126
12/10/48	60	8.0	...	4.0/3.8	Negative	...	70.4	....	...	Positive		156
12/17/48	...	....	...	.....	.....	...	....	....	...	.....		100
12/20/48	...	....	...	3.1/3.4	.....	8.1	85.0	1048	380	.....		94
1/3/49	70	8.3	3.1	.....	Negative	...	....	755	235	.....		
1/19/49	...	....	...	3.6/3.2	Negative	8.4	73.0	784	279	.....		
2/4/49	...	....	...	.....	.....	...	....	....	...	.....		107
2/23/49	...	....	...	4.0/3.5	.....	9.1	77.5	762	344	Positive		
4/27/49	...	....	...	.....	Negative	4.8	....	860	126	.....		190
5/11/49	...	....	...	.....	.....	...	....	825	635	.....		155
5/27/49	20	4.6	3.0	.....	.....	...	....	....	...	.....		
5/31/49	...	....	...	4.1/3.5	Negative	...	63.5	415	248	.....		245

a high carbohydrate and high protein diet with vitamin supplements, liver extract parenterally, choline and bile salts. There seemed to be some decrease in the intensity of the icterus but the remaining signs of obstruction persisted. His urine revealed 2+ albumin but was free of formed elements and sugar. The cholesterol levels reached a peak of 960 mg. per cent early in his course and persisted at about this level. Clinically the patient did not improve. In ten months of hospitalization he lost 45 pounds and nodules gradually appeared on the thighs and the palmar aspect of the fingers. A biopsy specimen of one of these nodules was diagnosed as benign xanthoma. No other member of his family is known to have had similar nodules at any time. For two weeks prior to admission to Goldwater Memorial Hospital (eleven months after the onset of jaundice and one month after the appearance of xanthomas) he noted marked polydipsia and polyuria. He gave no past or family history of diabetes.



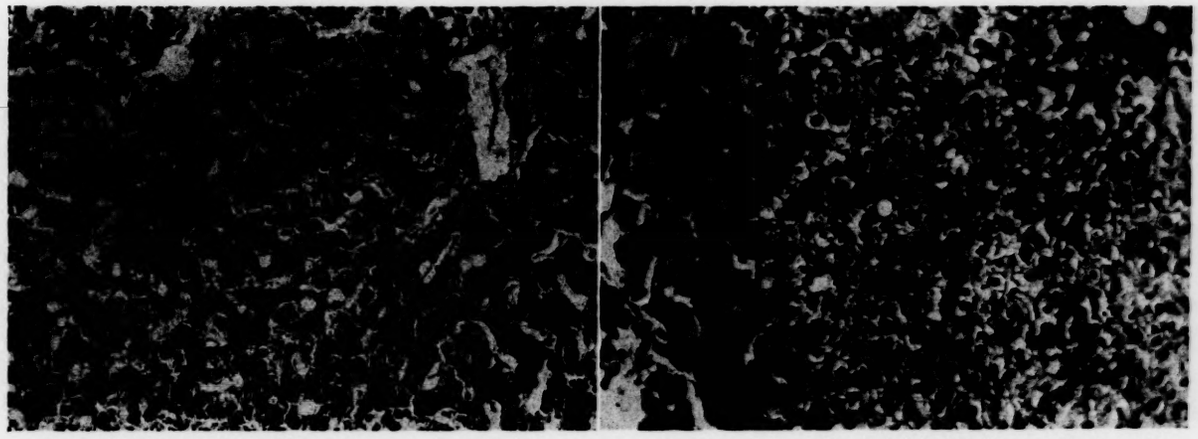
1 2

FIGS. 1 and 2. Photographs of the right ear and left knee showing multiple xanthomas.

On admission to Goldwater Memorial Hospital (November 5, 1948) his temperature was 98.4°F., blood pressure 142/98, pulse 84/minute and respiration 20/minute. The patient appeared undernourished, chronically ill and markedly jaundiced. Examination of the skin revealed many firm nodules, varying from pinhead to pea size with relatively yellow keratinized surfaces (Figs. 1 and 2), which appeared over the knees, elbows, ears, thighs and palmar aspect of the hands. The nodules were tender. There were no deposits in the axilla or on the eyelids. The sclerae were icteric. The fundi were normal. No lymphadenopathy was noted. The lungs were clear to percussion and auscultation. The heart was not enlarged. Regular sinus rhythm was present at a rate of 84/minute. There was a soft systolic murmur at the base of the heart. The abdomen revealed a right rectus scar. The liver percussed 3 cm. below the costal margin but the edge was not palpable. The spleen and kidneys were not felt. There was no shifting dullness or fluid wave. There was no peripheral edema or cyanosis. Rectal and neurologic examinations were normal. There was a scar on the penis.

The chest x-ray and gastrointestinal series were normal. The electrocardiogram revealed regular sinus rhythm with left axis deviation. An x-ray of the humerus revealed demineralization throughout the shaft with resorption of the trabeculae. The remainder of the bone films were normal. A red blood count was 3.8 million cells and hemoglobin was 11.6 gm. The white blood count was 11,900 with a normal differential count. There was no eosinophilia. The urine test for sugar was 4+ with no acetone, no albumin and no formed elements. A Mazzini test was negative. The fasting blood sugar was 263 mg. per cent and the blood urea nitrogen was 15.3 mg. per cent. An intravenous glucose tolerance test was diabetic in type (fasting blood sugar—250 mg. per cent, one-half hour—380 mg. per cent, one hour—390 mg. per cent, two hours—310 mg. per cent and three hours—358 mg. per cent). The albumin/globulin ratio was 3.4/4.7 gm. per cent. The total serum lipid was 8,500 mg. per cent with 4,400 mg. per cent as phospholipid. The total cholesterol was 1,875 mg. per cent with 353 mg. per cent as esters. The icterus index was 125, cephalin-flocculation test negative and the alkaline phosphatase 65.2 King-Armstrong units. The serum amylase was normal. The serum uric acid level was 2.7 mg. per cent. On admission a bone marrow differential count of 300 cells was essentially normal but revealed occasional large reticulo-endothelial cells filled with a meshwork of fine vacuoles thought to contain lipid. On subsequent bone marrow examinations, when the cholesterol levels were lower, these cells were no longer present. The patient was placed on a high carbohydrate, high protein diet with oral vitamins and 20 units of protamine zinc insulin daily.

His condition remained essentially the same until December 2, 1948, when two hours after a punch biopsy of the liver the patient went into shock. He was brought out of shock with repeated blood transfusions but in the succeeding



3 4

FIG. 3. Photomicrograph of the surgical biopsy of the liver two months after the onset of jaundice, showing liver cell necrosis and an increase in fibrous tissue, × 300.

FIG. 4. Photomicrograph of the punch biopsy of the liver twelve months after the onset of jaundice showing a pericholangiolitic type of biliary cirrhosis with bile stasis; × 300.

days he complained of a constant right upper quadrant pain associated with temperature elevations to 102°F. On December 14, 300 cc. of clotted blood was removed from the right pleural cavity. The subdiaphragmatic space was normal. Following this he made an uneventful recovery. Postoperatively, however, it was noted that he required no insulin. His fasting blood sugar and glucose tolerance curve were as follows (January, 1949): fasting—107 mg. per cent, one-half hour—119 mg. per cent, one hour—179 mg. per cent, two hours—164 mg. per cent and three hours—93 mg. per cent.

The icterus has persisted and the cephalin-flocculation test has remained negative. His alkaline phosphatase has remained elevated but the total cholesterol levels have fallen to 415 mg. per cent at the time of writing. The total lipids are now 2,400 mg. per cent and the phospholipids are now 1,062 mg. per cent. The xanthomas have increased in number and recently have become quite painful. His diabetic condition gradually returned and he now requires 20 units of protamine zinc insulin daily.

A surgical biopsy of the liver two months after the onset of jaundice (Fig. 3) revealed a marked increase in the fibrous tissue with division of the parenchyma into irregular lobules. There was necrosis of the parenchymal cells suggesting an acute process. The node removed at operation revealed a large number of foam cells presumably filled with lipid.

A punch biopsy of the liver twelve months after the onset of jaundice revealed a mild but definite increase in periportal connective tissue. (Fig. 4.) Within this tissue were many polymorphonuclear cells and fewer lymphocytes. The polymorphonuclear cells in some areas were segregated in clumps bordered by connective tissue. Bile ducts were comparatively rare but one, cut in longitudinal section, had bile-stained epithelium and a few polymorphonuclear cells within the wall. The connective tissue surrounded isolated small groups of parenchymal cells in many areas. One central vein seen showed marked congestion of the sinusoids about it. The parenchymal cells were well preserved but in the periportal areas there was marked bile stasis with large inspissated plugs in the bile canaliculi and lighter brown pigment in the liver cells. Even in these cells necrosis was not seen. The remainder of the parenchymal cells had a fairly regular arrangement. There were several binucleated cells and cells with large hyperchromic nuclei. The Kupffer cells were laden with bile pigment. One isolated clump of cells had clear cytoplasm suggesting lipid. Fat stains showed a moderate amount of sudanophilic material diffusely distributed throughout the small amount of tissue available for frozen section. Much of it appeared in portions of the cytoplasm bordering the sinusoids: A small amount was definitely within Kupffer cells. The bile pigment remained unstained. The diagnosis of the section was biliary cirrhosis of the cholangiolitic type.

In summary, the patient is a fifty-four year old colored male who received a total of four injections of arsenic intravenously in three weeks' time and immediately became deeply

jaundiced. The jaundice and associated signs of an obstructive type of liver disease have persisted until the present time. He noted xanthomas ten months following the onset of jaundice and clinical diabetes one month after the appearance of the xanthomas. The most recent liver biopsy revealed a cholangiolitic biliary cirrhosis.*

COMMENTS

The cases of postarsphenamine obstructive jaundice described by Hanger and Gutman[2] are characterized by: "(1) Acute onset with constitutional and gastrointestinal symptoms coming on several hours after the second or third intravenous arsenical injection. (2) Appearance within several days of jaundice which may persist for weeks or months unaccompanied by other symptoms except pruritus. (3) Indications by various laboratory criteria of obstructive jaundice with little or no evidence of liver cell degeneration. (4) Preservation of essentially normal parenchyma in liver biopsies, the principal lesion being pericholangitis and bile thrombi in the finer biliary radicles. (5) Eventual recovery of the patient."

In an analysis of 147 cases of postarsphenamine jaundice occurring at Johns Hopkins University Hospital, Soffer[3] found 37 per cent occurring during or after completion of the first five injections. In another large series of cases of postarsphenamine jaundice about 80 per cent of the cases occurred within two and one-half months after the last injection.[5] Of 113 cases of postarsenical jaundice reported by Genner[4] ten had their onset during the first three weeks. In Wile and Sams' series[6] two peaks of onset were noted, one at the fifth day and one at the ninety-sixth day after the last injection. They reported that about 66 per cent of their cases of postarsphenamine jaundice occurred on the average of eighty days after the last injection. Thus it can be seen that there is wide variation in the number of cases showing the onset of jaundice early in the course of therapy. In none of the above series except Hanger and Gutman's was a distinction made between obstructive and hepatocellular jaundice but in all probability a number of the cases of early jaundice with onset during the first three weeks of arsenic therapy were of the obstructive type.

In most of Hanger and Gutman's twelve cases the first injection was without incident but definite symptoms and signs of a constitutional reaction characterized by chills, fever, anorexia, nausea, muscular pains and weakness were noted after the second or third injection. The jaundice was predominantly of the obstructive type with high alkaline phosphatase levels, normal cephalin-flocculation tests, high serum cholesterol levels and bile in the urine with little or no urobilinogen. The clinical and laboratory evidence of obstructive jaundice persisted in these cases for as long as seven months but eventually all made full recovery of hepatic function. Subsequent case reports of intrahepatic biliary obstruction following arsenic therapy substantiate this view.[7–13]

The most prominent features of the pathology of postarsenical obstructive jaundice as noted by Hanger and Gutman[2] were the lack of significant parenchymal damage in the liver and the presence of a cholangiolitis and pericholangitis with bile plugs in many of the bile capillaries. There were inflammatory changes about the bile passages. These findings differ from those seen with the delayed type of jaundice in which there is marked alteration of the normal architecture of the liver parenchyma.

It has been postulated that the obstructive jaundice following arsenical therapy is an allergic manifestation to arsenic.[2] It is often associated with so-called "erythema of the ninth day." Genner[4] found evidence of the skin manifestations of erythema of the ninth day in three of ten patients who had jaundice within the first three weeks. Hanger and Gutman[2] noted a scarlatiniform erup-

* Since writing this case report a period of six months has elapsed. In this time almost all of the patient's xanthomas have disappeared. His cholesterol level now ranges between 300 to 350 mg. per cent and his alkaline phosphatase remains elevated (50–60 K.A. units). The diabetes mellitus persists.

tion in six of their twelve cases but did not consider this erythema of the ninth day. Peters[14] in an extensive review of thirty-six cases of erythema of the ninth day noted jaundice in 13 per cent and lymphadenophathy in 76 per cent of the cases. He was impressed with the general constitutional reactions of the patients: fever, muscle pain, anorexia, weakness and the variability of the skin manifestations. The onset of the symptoms was usually between the fifth and nineteenth day after the first injection of arsenic. Peters believed that the skin manifestations, jaundice and constitutional symptoms were all part of a systemic reaction to arsenic, with the allergic manifestations varying in different patients. Similar systemic and skin manifestations were noted following the use of antipyrine, salicylates, sulfonamides, barbiturates and quinine.[14]

An eosinophilia of 5 per cent or greater was noted in 44 per cent of Peters' cases of erythema of the ninth day.[14] Hanger and Gutman[2] noted that five of their cases had an eosinophilia of over 5 per cent. In Sofer's[3] series five of thirty-two cases of jaundice occurring before the fifth week had an eosinophilia of over 10 per cent. The early and abrupt onset of the constitutional symptoms, the small dose of arsenic necessary to produce the reaction and the presence of eosinophilia make one suspect that postarsenical obstructive jaundice is an allergic manifestation to arsenic rather than an infectious or toxic process.

The delayed type of jaundice following arsenical therapy is usually of the hepatocellular variety and chemical studies are indicative not of obstruction, but of liver-cell inflammation and necrosis. It has been repeatedly postulated that this delayed jaundice is the result of infectious or serum hepatitis transmitted by syringe, or coincidental infectious hepatitis.[15–18]

In our case most of the criteria set up by Hanger and Gutman[2] can be met either in full or in part. Our patient's symptoms began with the first injection of arsenic and recurred after each of the three subsequent injections. He received a total of four injections of arsenic in three weeks. The initial constitutional symptoms consisted of anorexia, muscle pain, fever and weakness. Jaundice was first noted after the fourth injection and has persisted until the present time (seventeen months). No skin manifestations (erythema) were observed. At the onset of jaundice in our patient the cephalin-flocculation test was 4+. In about three months it had returned to normal. It was during the initial three-month period when the cephalin-flocculation test was 4+ that the surgical biopsy was taken. Its appearance would suggest rather marked hepatocellular necrosis and subsequent fibrosis. This pathologic process is not usually seen in the purely obstructive type of postarsenical jaundice, and possibly at this early stage an active process was going on in the liver. The punch biopsy of the liver taken one year later revealed the characteristic pathologic picture as initially described,[2] and very little evidence, if any, could be seen for an active liver-cell necrosis. Rather the main abnormality seemed to be cholangitis and cholangiolitis with bile stasis.

Throughout the patient's course (except for the initial 4+ cephalin-flocculation) his jaundice has been almost exclusively of the obstructive type. His alkaline phosphatase determinations and serum cholesterol levels have been high. He has had bile in his urine with little or no urobilinogen until recently when urobilinogen has been present in the urine in normal or slightly elevated titers. His serum albumin was low and globulin high at times but not at present. Following the early positive cephalin-flocculation tests these have been repeatedly negative. His thymol turbidity test has been normal or slightly above normal. The abnormally high total serum cholesterol levels and the icterus index have gradually decreased but the alkaline phosphatase has remained at about the same level. Nothing definite can be said as to the ultimate prognosis of his liver disease.

About nine months after the onset of jaundice our patient developed marked xanthomatosis. His serum cholesterol values

had been elevated since the onset of his jaundice and reached a peak of 1,953 mg. per cent exactly one year after the first injection of arsenic. The xanthomas have been increasing in number and are extremely painful. The total lipids on admission were 8,500 mg. per cent and the phospholipid 4,400 mg. per cent, both extremely high levels. At present the total lipids are 2,400 mg. per cent and the phospholipids 1,062 mg. per cent. In five of the twelve cases reported by Hanger and Gutman[2] the total serum cholesterol was raised and in one instance reached 3,100 mg. per cent without evidence of xanthomatosis. Chanutin and Ludewig[19] in 1937 reported a case of postarsphenamine jaundice with a serum cholesterol level of 1,480 mg. per cent and xanthomatosis. Their patient received a total of six intravenous injections of arsenic before the onset of jaundice and made a full recovery in two years. Peters[14] describes two cases of obstructive jaundice following arsenical therapy with elevated cholesterol levels without xanthomatosis. In two[7,9] of the more recently reported cases of postarsphenamine obstructive jaundice the serum cholesterol levels were normal. In many of the other cases of postarsphenamine jaundice the serum cholesterol levels were not reported. In a case of postarsenical obstructive jaundice with xanthomatosis reported by Bockus[10] there was some indication of antecedent liver damage about fourteen years prior to the administration of arsenic. The patient received three injections of arsenic and subsequently developed an obstructive type of jaundice and nodular xanthomas. Her highest cholesterol value was 1,775 mg. per cent. She made an uneventful recovery with gradual disappearance of the jaundice and xanthomas.

Extremely high serum cholesterol levels with xanthomatosis and obstructive jaundice have been described by Thannhauser and others[20,21] for many years as xanthomatous biliary cirrhosis. Initially it was believed that the hypercholesterolemia precipitated deposits in the biliary system and caused xanthomatous scar tissue giving rise to the obstructive phenomenon.[20] However, in recent years autopsy and biopsy examinations have failed to disclose such intrahepatic xanthomatous deposits but rather have revealed a pericholangiolitic type of biliary cirrhosis.[22,23] If the history of arsenic administration were lacking or overlooked in our case, it would fit in well with the general picture of xanthomatous biliary cirrhosis as outlined by Thannhauser and MacMahon.[23] The pathologic picture is essentially the same: a pericholangiolitis with intralobular bile stasis and a lack of parenchymal involvement. Eppinger[24] and Watson[25] have noted similar lesions in cases of catarrhal jaundice either of viral or unknown etiology. As a matter of speculation, possibly a number of cases of xanthomatous biliary cirrhosis are the result of an initial allergic reaction to some drug or toxic agent resulting in intrahepatic obstructive jaundice with hypercholesterolemia and xanthomatosis. The predominance of females and the gradual onset of the jaundice in the cases of xanthomatous biliary cirrhosis, however, would remain unexplained.

An interesting finding in our case on admission was the presence of 4+ sugar in the urine and a fasting blood sugar of 250 mg. per cent. An intravenous glucose tolerance test was abnormal. For a short time in December, 1948, the patient's urinary and fasting blood sugars were normal but at present he requires 20 units of protamine zinc insulin to control his diabetes. The etiology of the diabetes in this case is a matter of speculation. Arsenic has occasionally been indicted as the cause of pancreatic necrosis in cases of poisoning.[26] However, in animal studies it has been shown that arsenic has no special affinity for the pancreas such as it has for the liver and kidneys.[27] Xanthomatous deposits in the pancreas or a chronic pancreatitis could be incriminated but to date there is little if any evidence to support this concept. In the case of obstructive postarsenical jaundice reported by Freis and Mater[7] a sprue-like syndrome supervened

with flattening of the glucose tolerance curve, indicating some pancreatic dysfunction. In this case the cholesterol was at the upper limit of normal and there were no xanthomas present. In the remainder of the cases of postarsenical obstructive jaundice reported the fasting blood sugars have been normal.

Our patient was put on a high protein, high carbohydrate diet with vitamin supplements. Previously he had received bile salts, choline and methionine without effect. BAL (2–3 dimercaptopropanol) has been used successfully in the treatment of the various manifestations of arsenic poisoning but to date there are only a few conflicting reports on the effect of BAL on postarsenical jaundice.[28,29] It has been used mainly in delayed or hepatocellular jaundice and the action on the obstructive type of postarsenical jaundice has not been evaluated.

SUMMARY

1. A case of postarsenical jaundice of the obstructive type with complicating xanthomatosis and diabetes mellitus is presented.

2. An allergic reaction to arsenic has been postulated as the cause of the obstructive jaundice.

3. The occurrence of xanthomatosis with intrahepatic obstructive jaundice of known and unknown etiologies is discussed.

Dr. Margaret Bevans was kind enough to review the slides for us and we wish to express our thanks to her. Dr. Lester Besen was instrumental in obtaining the records of this patient's early hospitalization.

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Cholangiolitic Cirrhosis with Intrahepatic Biliary Tract Obstruction and Xanthomatosis*

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An occasional patient with chronic obstruction of the biliary tract from any one of several causes develops xanthomatosis. This complication is well known as a sequel to obstruction of the common duct by stone. It may occur also in unusual cases of intrahepatic biliary obstruction in the absence of obstruction to the larger bile ducts.

Thannhauser and his associates have written extensively on xanthomatous biliary cirrhosis,[1,2] a syndrome characterized by the appearance of skin xanthomas in patients with chronic biliary tract obstruction. Additional features include enlargement of the liver and spleen and a marked elevation in serum cholesterol and lecithin without visible lipemia. These authors have adopted the view that such patients suffer from a primary disturbance in lipid metabolism at the cellular level, i.e., there is overproduction of lipids in the tissues, the increased serum lipids result from this overproduction, the skin xanthomas represent intracellular accumulations of lipids and the liver disease is initiated by xanthomatous involvement of the intrahepatic biliary tract, leading to obstruction and consequent biliary cirrhosis. Histologic evidence for this mechanism in the production of liver disease is wanting, however, as pointed out by MacMahon[3] in a study based upon material from some of Thannhauser's cases as well as from other reports in the literature.

A second approach to the problem of associated xanthomatosis and chronic obstruction of the biliary tract is based upon the fact that hepatotoxic agents occasionally produce a form of liver disease characterized by what appears to be intrahepatic biliary obstruction. A large proportion of these patients exhibit very high serum lipid values and an occasional patient has been observed to develop xanthomatosis. Hanger and Gutman[4] described twelve cases of jaundice apparently due to intrahepatic biliary tract obstruction following the administration of arsphenamine. In contrast to the usual clinical and histologic picture of postarsphenamine hepatitis, these cases showed little evidence of parenchymal damage. The typical case in this unusual group showed jaundice with dark urine and clay-colored stools, increased serum bilirubin and alkaline phosphatase, with a negative cephalin-flocculation reaction. Biopsy specimens were remarkable for the paucity of histologic change, exhibiting only pericholangiolitis and bile plugs in the canaliculi. Five of the twelve cases showed serum cholesterol levels exceeding 400 mg. per cent. When serial studies could be carried out, it was apparent that the cholesterol rise reached its maximum after the serum bilirubin and alkaline phosphatase had begun to decline. None of these patients developed xanthomatosis. However, Chanutin and Ludewig[5] reported a case of xantho-

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matosis which occurred three years following the development of prolonged hepatitis in the course of arsphenamine injections. Stolzer and others[6] have reported a similar case.

Infectious hepatitis of viral origin may produce a similar picture. In this connection, Watson and Hoffbauer[7] reviewed the particular problem of cholangiolitic hepatitis and presented eight cases. These patients exhibited, at least in some phase of their illness, manifestations of regurgitation jaundice with little other evidence of liver disease, as determined by their composite study. As had been observed in the unusual reaction to arsphenamine, the histologic change in the liver parenchymal cells was minimal. Two of the eight patients exhibited cholesterol levels in excess of 400 mg. per cent. None of them developed xanthomatosis.

It would appear, then, that at least two agents which ordinarily cause diffuse destruction of the parenchymal cells of the liver may produce a highly selective lesion causing intrahepatic obstruction to the biliary tract. There is an associated disturbance in lipid metabolism marked by increased cholesterol and phospholipid concentration in the plasma, and occasionally by xanthomatosis to give the characteristic syndrome of xanthomatous biliary cirrhosis. The specific nature of the hepatic lesion is obscure but it appears to be a cholangiohepatitis.[7] The relationship between the disturbance in lipid metabolism and the intrahepatic biliary tract obstruction is not clear; the time relationship described by Hanger and Gutman[4] suggests that this relationship may be complex.

The following case report is based upon an eight-year study, with postmortem findings, in a patient with chronic liver disease who developed xanthomatosis.

CASE REPORT

M. S., a fifty-two year old housewife, first entered the Presbyterian Hospital in November, 1940, because of a flare-up of chronic rheumatoid arthritis, and the discovery in the clinic of enlarged liver and spleen. Past medical history included epistaxis, beginning in early childhood, increasing in severity following the menopause. These required packing or cauterization on more than eighty occasions. There was no history of easy bleeding from any other source. A complete physical examination in 1934, prompted by the repeated epistaxes, contains specific denial of enlargement of liver or spleen. The patient had also suffered two distinct attacks of arthritis with complete recovery: one at the age of eleven, involving principally the left ankle, and the other at the age of thirty-two, affecting the small joints. This second attack had been the occasion for taking some ten or fifteen tablets of a neocinchophen preparation. The patient could recall no skin eruption or jaundice following the use of this drug. The recurrence leading to the present admission began two years previously and eighteen years after the second attack of arthritis. Along with fleeting joint pains she noted undue fatigue and weight loss of 15 pounds. On application for treatment at the arthritis clinic the patient had been given a trial of irradiated ergosterol, with good results. Hospital admission was recommended, however, because of the incidental finding of a striking elevation in the serum alkaline phosphatase and the subsequent finding of enlarged liver and spleen. It is of interest that a daughter of the patient had severe rheumatoid arthritis and that a son had suffered two attacks of rheumatic fever.

On examination the patient did not appear sick. Salient findings were: moderate rheumatoid deformity of the fingers, wrists, elbows, ankles and knees; smooth, firm liver edge, palpable at the level of the umbilicus, and an enlarged spleen. Note was also made of cystocoele and prolapsed uterus.

Laboratory studies yielded the following results: Blood morphology and routine urine examination were within normal limits. A serologic test for syphilis was negative. Significant abnormalities were: alkaline phosphatase 36 Bodansky units per cent, total cholesterol 290 mg. per cent, serum globulin 4.2 gm. per cent and a bromsulphalein retention of 40 per cent thirty minutes after the administration of 5 mg. per kg. Important normal values were those obtained for serum albumin, bilirubin, negative cephalin-flocculation test and prothrombin time. (Table 1.) Additional studies of bleeding time, clotting time, capillary fragility and of blood

platelets failed to incriminate any of these as the basis for the epistaxes. Roentgenographic examination of the skeleton failed to disclose any evidence of bone disease that could account for the elevated alkaline phosphatase. Barium studies of the upper and lower gastrointestinal tract revealed diverticulosis coli but no evidence of neoplasm. The patient was discharged with a diagnosis of rheumatoid arthritis with possible Felty's syndrome, a diagnosis which was acknowledged to be unsatisfactory.

A period of three and one-half years ensued marked by little change in the patient's condition. From the records of periodic visits to the clinic it can be learned that she experienced a slow weight gain of 10 pounds, only to lose it; the irradiated ergosterol was effective in the alleviation of joint pains; and that the serum alkaline phosphatase persisted irregularly at a high level. (Table 1.) A complete re-evaluation in February, 1944, the occasion of a pelvic repair operation because of dysuria, yielded a clinical and laboratory picture remarkably similar to that of November, 1940.

The period from May to October, 1944, witnessed the gradual development of obstructive jaundice. Fleeting jaundice and acholic stools were noted that spring. The jaundice became

TABLE 1

	Serum Bilirubin (mg. %)	Alkaline Phosphatase (Bodansky units %)	Serum Albumin (gm. %)	Serum Globulin (gm. %)	Total Cholesterol (mg. %)	Ester Cholesterol (mg. %)	Cephalin Flocculation	Prothrombin Time (sec.)	Urine Urobilinogen (mg./hr.)	BSP Retention, 30′ (%)
1940 Oct.	0.5	40	4.2	4.3	397	.....	0	12	.....	40
Nov.	....	36	4.0	4.2	290					
1941 Jan.	....	32								
Mar.	....	37								
Sept.	....	38								
Dec.	....	27								
1942 Mar.	....	28								
1943 Jan.	....	17	...	...	340					
1944 Feb.	0.5	42	4.5	4.5	417	.....	0			
Mar.	0.5	34	4.3	5.8	446	.....	±	21		
Apr.	....	..	...	...	....	.....	..	18		
June	0.8									
Dec.	3.9	39	3.6	4.1	530	.....	0	25		
1945 Jan.	3.7									
July	2.9	..	3.8	5.1						
1946 Mar.	7.1	51	3.0	5.2	625	.....	0	30		
Apr.	6.1	45	3.4	5.1	557	511	0	23		
May	....	..	...	...	....	.....	3	..	0.37†	55
June	4.1	..	3.4	4.7	613	115	3	19	0.23	
July	5.1	..	...	...	675	138	4	..	0.27	
Nov.	1.3	..	3.2	4.7	603	143	4			
1947 Jan.	2.4	..	3.3	4.7	....	.....	4	16	0.21	
Feb.	2.1	..	3.2	4.6	328	74	4			
Mar.	2.4	..	...	...	305*	83	3	..	.....	9
Apr.	9.6	..	3.3	5.1	307	91	0	19	0.27	
May	11.4	..	2.6	5.2	284	60	2	21		
June	9.0	..	3.3	5.3	....	.....	0			
July	5.9	..	...	...	....	.....	3	..	.....	21
Sept.	7.7	..	3.1	5.2	397	85	4			
Oct.	7.3	..	...	...	....	.....	4	..	0.54	
Nov.	7.6	..	3.2	4.9	338	98	3	..	.....	21
Dec.	7.3	35	...	...	333	94				
1948 Jan.	8.1	..	2.5	5.3	312	80	..	18	0.19	

* The serum specimen obtained in March, 1947, contained total lipid 1,430 mg. per cent and lipid phosphorus 21 mg. per cent.

† These values fall within the range of normal for this laboratory.

obvious by August and about this time she noted the urine to be dark-colored. She experienced occasional twinges of pain in the right upper quadrant. She was readmitted in December, 1944. In addition to jaundice, it was noted that the spleen had increased in size over that of the previous admissions. There was slight pretibial edema but no ascites. In contrast to previous findings, the bilirubin was 4 mg. per cent, bile was present in the urine and the prothrombin time was 25 seconds. (Table 1 and Fig. 1.) An exploratory operation was performed by Dr. Allan Whipple, although the likelihood of common duct obstruction was admittedly small. The operative note reads in part, "Liver enlarged . . . surface was smooth and of normal color . . . more firm consistency than normal. The gallbladder was grossly normal and no stones could be palpated within it. The pancreas was slightly indurated but not strikingly pathological." A punch biopsy was reported by Dr. A. P. Stout as showing "fibrosis of portal areas, not marked, extending into liver lobules. No proliferating bile capillaries. Marked infiltration with lymphocytes and some histiocytes." The patient was subsequently discharged with a diagnosis of cirrhosis of the liver.

The patient's condition deteriorated markedly in the course of the following year. She developed severe anorexia. The eating of even small amounts of food led to distention and nausea. Stools were frequent, bulky and clay-colored and jaundice persisted. Several flat, yellow, waxy deposits appeared in the skin of the eyelids, fingers and palms. Her readmission to the Presbyterian Hospital in March, 1946, was precipitated by a week of continuous bleeding from the nasal septum. Findings on examination were marked emaciation and weakness, xanthelasma and xanthomas involving the eyelids, fingers and palms, several subcutaneous nodules along the ulnar border of the right forearm, enlarged liver and spleen as previously and, along with the old rheumatoid deformities, increased warmth with signs of fluid in both knee joints. The nasal bleeding arose from the usual site in the septum, now marked by perforation.

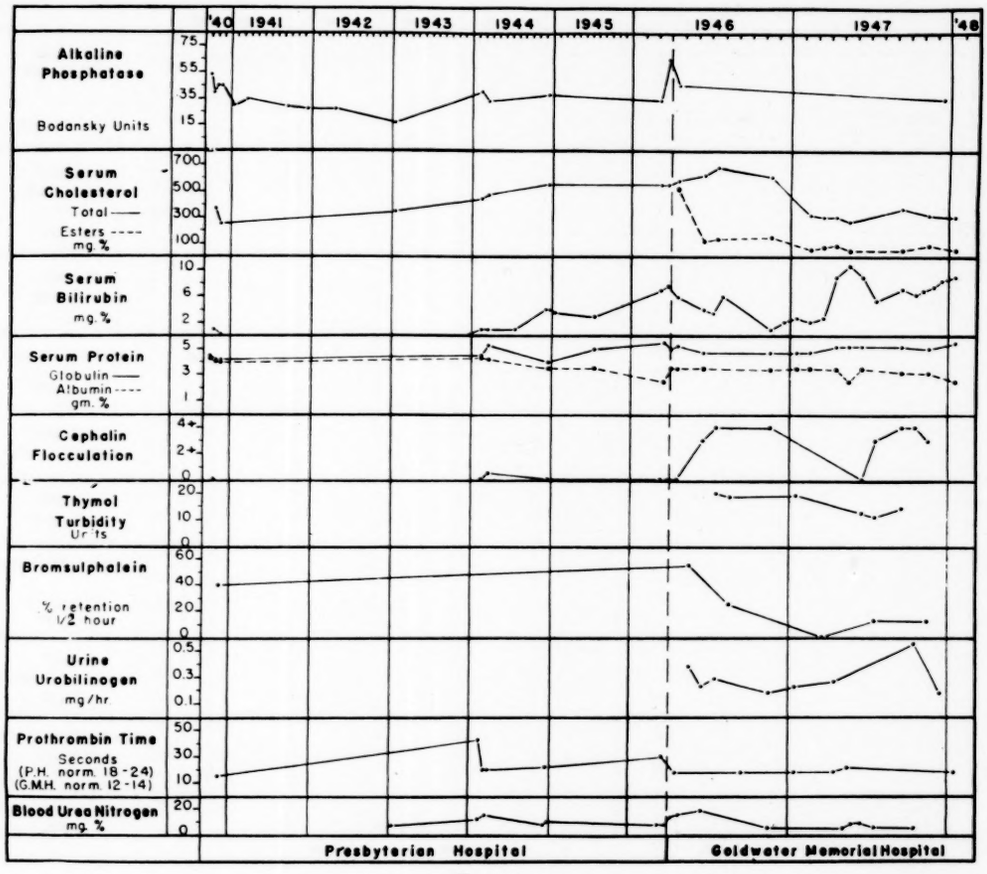

FIG. 1.

Laboratory studies showed few changes: blood hemoglobin 10 gm. per cent, and 2 plus proteinuria on several specimens. Rectal temperatures sustained at about 100°F. marked the patient's entire stay. A concerted effort was made to help the patient's nutritional status: she was encouraged to eat a highly nutritious diet, supplemented by brewers' yeast, liver extract and vitamin preparations. Arrangements were made for the patient's transfer to the Columbia Research Division of Goldwater Memorial Hospital, where it was possible to continue the program of care and study for the two years that the patient survived.

The first six months saw some improvement in the obstructive picture, with an irregular decline in the serum bilirubin level and with the appearance of normally colored stools, together with partial relief from postprandial distention and nausea, and from the frequency of bowel movements. The remission was short lived. Anorexia became marked, and with the extreme wasting pressure sores appeared. The last month of her illness she dozed frequently but could always be roused. Death was quiet, without terminal episode.

Autopsy was performed eight hours postmortem. The skin and sclerae were deeply icteric. Waxy yellow plaques were present over periorbital regions, forearms and hands; a single subcutaneous nodule was attached to the right olecranon bursa. The chest contained 100 cc. of bile-stained fluid in each pleural space and old fibrous pleural adhesions. The pulmonary arteries were streaked with atheromatous plaques down to the finest radicles. The lungs were normal. The pericardial space was obliterated by dense fibrous adhesions. The heart weighed 190 gm. and was not dilated. In the epicardium of the left auricle were numerous atheromatous deposits. The mitral ring was thickened and calcified. At the base of the anterior leaflet were confluent atheromatous plaques. White pinpoint atheromas studded the line of closure. The chordae tendineae were discrete. The aortic valve ring was slightly thickened and atheromas accentuated the tubercles of Arantius. All branches of the coronary arteries contained numerous arteriosclerotic plaques, none of which occluded the lumen. Small areas of fibrosis dotted the myocardium of the left ventricle in the apex and in the interventricular septum.

Microscopically, sections of the left auricle presented a bizarre appearance. Aggregations

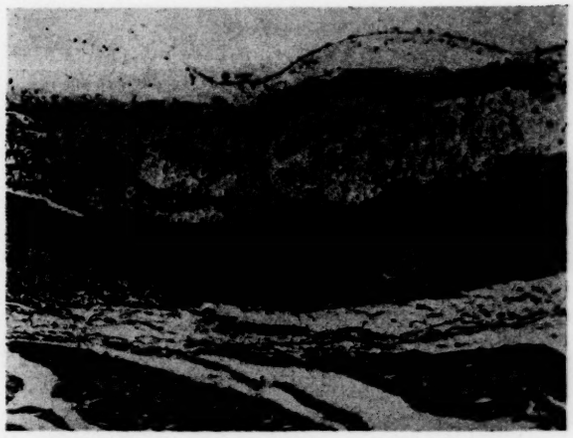

FIG. 2. Plaque in endocardium of left auricle showing foam cells and fibrosis; hematoxylin and eosin stain × 152.

of huge foamy cells separated the layers of endocardium. (Fig. 2.) Lymphocytes and Anitschkow myocytes surrounded them. In a few areas the endocardium was thickened only by collagenous tissue which was relatively acellular. With special stains, fat was abundant in the foam cells but the elastic fibers showed little alteration. None of these plaques bore any resemblance to MacCallum's patches. The only myocardial lesions outside of areas of fibrosis noted grossly were in the interauricular septum where many of the myocardial fibers were atrophied and foam cell infiltration similar to that described in the left auricular endocardium was noted. Sections of the mitral and aortic valves showed calcification of the rings and large amounts of atheromatous material in the valve cusps. The aorta was remarkably elastic despite the large amount of atheromatous material deposited in the intima. The arteriosclerotic plaques in the major vessels ended within a few centimeters of their origins except in the iliac vessels where the plaques continued into the hypogastric and femoral arteries. None of the corresponding large veins contained atheromas.

The abdominal cavity contained 3,000 cc. of bile-stained clear fluid. Dense fibrous adhesions extended between the viscera and parietal peritoneum. The liver was 6 cm. below the costal margin in the right parasternal line but above the costal margin elsewhere. It was small but heavy, weighing 1,550 gm. The lobar contours were not distorted. The outer and cut surfaces were finely nodular and deeply bile-stained. The portal vein was not unusual. The intrahepatic bile ducts transported small amounts of golden thin bile and were of normal caliber.

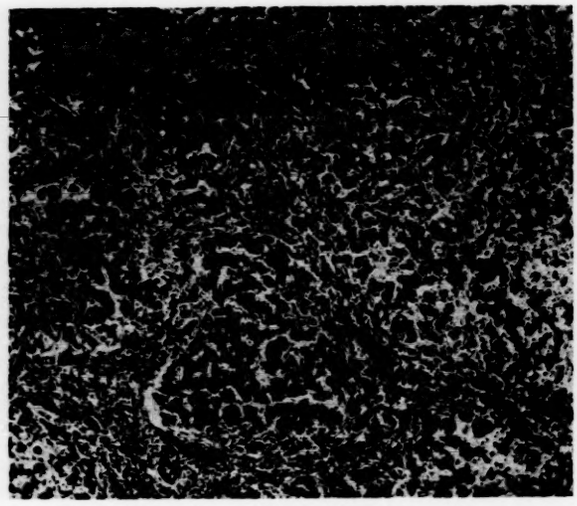

FIG. 3. Liver showing periportal fibrosis with extension of connective tissue into the lobules; no bile ducts are seen in the portal areas. The dark cells adjacent to and surrounded by fibrous tissue are filled with bile pigment; trichrome stain × 126.

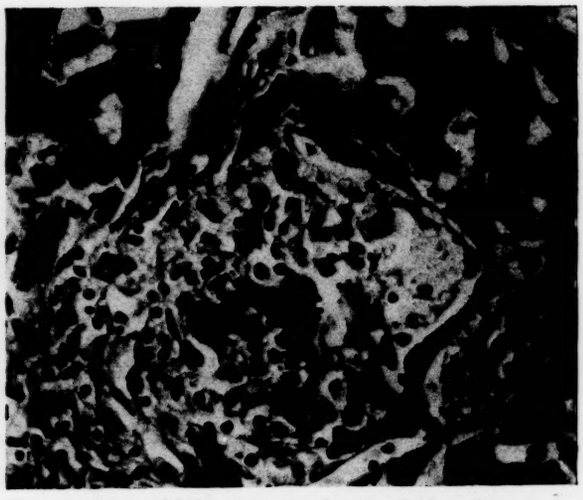

FIG. 4. Area of bile necrosis about a large plug; note good preservation of the liver cells outside of the area of necrosis; hematoxylin and eosin × 688.

The gallbladder was distended with 100 cc. of bile similar to that within the liver. The wall of the gallbladder was thin and the mucosal pattern uniform. No cholesterolosis or stones were present. The extrahepatic bile ducts were entirely normal.

Numerous sections from various parts of the liver had a uniform appearance. Increased amounts of periportal connective tissue divided the parenchyma into small irregular lobules. The connective tissue bands were often hyalinized and heavily infiltrated with foam cells, polymorphonuclear cells and lymphocytes. Fine connective tissue fibrils extended from the periportal areas into the parenchyma outlining and thickening the walls of the sinusoids. Lack of bile duct proliferation and the scarcity of small bile ducts in the periportal connective tissue was striking. The liver cells and the bile canaliculi were distended with bile, particularly in the parenchyma adjacent to the periportal areas. (Fig. 3.) In many areas about the bile plugs the parenchymal cells had undergone necrosis. The bile pigment was dense and deep brown having an inspissated appearance. (Fig. 4.) In contrast to the dissolution of parenchymal cells seen in patients dying of liver insufficiency with postnecrotic cirrhosis and occasionally with Laennec's cirrhosis, the parenchymal cells were remarkably well preserved and orderly in arrangement. The lumens of the sinusoids in many places appeared occluded by the presence of Kupffer cells and endothelial cells greatly distended with bile pigment and foamy cytoplasm. Reticulum stains showed preservation of the framework even in the areas of bile necrosis. With fat stains only a few areas showed any demonstrable lipid within the liver cells. The Kupffer cells, despite their foamy appearance, contained only a small amount of sudanophilic material. In the areas of bile necrosis there were, of course, many fat-laden phagocytes. The bile duct epithelium and gallbladder mucosa were singularly free of fat droplets.

The spleen weighed 450 gm. The pulp was dark red and firm. Throughout the pulp circumscribed areas of bile-containing foam cells which stained with sudan were found. (Fig. 5.) Lipid infiltration of the arteries and arterioles were marked but little fat was observed in the reticulo-endothelial cells of the malphigian bodies.

No varices were present in the esophagus. The only abnormality in the gastrointestinal tract was diverticulosis of the colon. The kidneys were of normal size with a smooth surface. The medullary rays were accentuated by yellow streaks which extended into the sharp pyramids. Microscopically, cortical scarring was evident. In these areas were bile-stained and hyalin casts. The epithelium of the convoluted tubules was heavily pigmented with bile while that of the collecting tubules was unusually high. With sudan stain, varying amounts of fat were present within the tubular epithelium, most marked in the loops of Henle. The pelvis was thickened and many lymphocytes and lymph follicles were present beneath the intact epithelium.

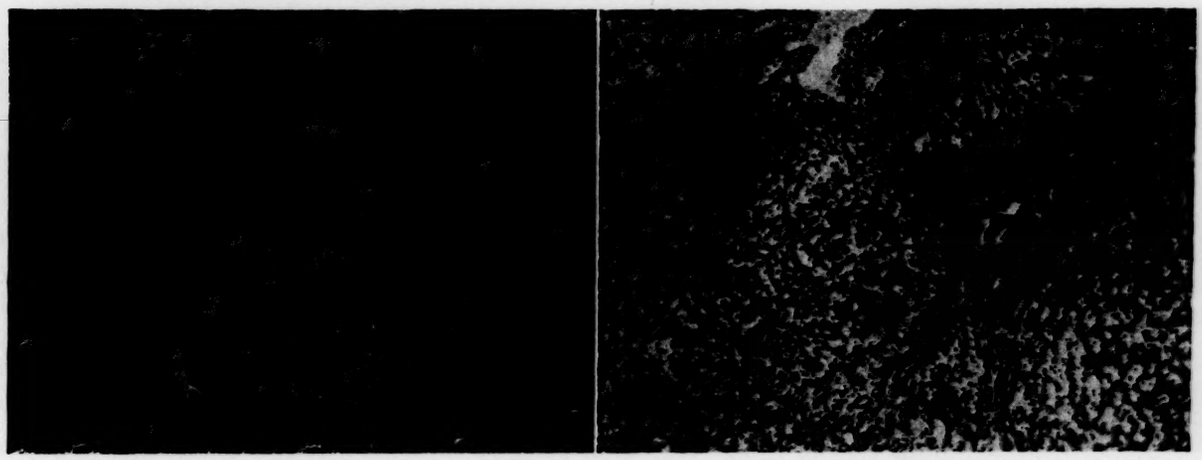

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FIG. 5. Circumscribed area in spleen containing large foamy cells which are bile-stained; hematoxylin and eosin stain × 177.

FIG. 6. Biopsy No. 2595, Presbyterian Hospital; note bile plugs in lobules bordering on the bands of periportal connective tissue. (For contrast with Figure 3.) Hematoxylin and eosin stain × 126.

The bladder was thin-walled and the mucosa the site of cystitis cystica. The thickened uterine arteries contained large amounts of stainable lipid. The adrenals were small and the cortical lipid was depleted. The lymph nodes throughout the body were enlarged and discrete. Those of the periportal and peripancreatic region were filled with bile pigment and foam cells. The sternoclavicular joint showed changes consistent with rheumatoid arthritis; joints of the extremities could not be examined. Generalized osteoporosis of the ribs, sternum and vertebrae was present. Permission for examination of the brain was not obtained.

Anatomic diagnosis included: portal cirrhosis (cholangiolitic type), splenomegaly, xanthomatosis, anasarca, bile and lipid nephrosis, chronic pyelonephritis, rheumatoid arthritis, generalized arteriosclerosis and adhesive pericarditis.

COMMENT

This case presents several features of unusual interest in connection with the origins of cholangiolitic cirrhosis, the relation of xanthomatosis to biliary tract disease and the association of atheromatosis with hypercholesterolemia.

The onset of the disease cannot be fixed with certainty; the initial discovery of hepatosplenomegaly was accidental, and the course during the first four years was nearly asymptomatic although chemical studies indicated sustained elevation of serum alkaline phosphatase, cholesterol and globulins. The second four years were marked by manifest obstructive jaundice, xanthomatosis and wasting illness leading to the patient's death. The etiology of the disease is not clear. The only exposure to a hepatotoxin was the ingestion of neocinchophen eighteen years before the first recognized evidence of liver disease. In his review of cinchophen compounds, Hueper[8] assembled ten cases of fatal liver disease due to neocinchophen. As in toxicity associated with the parent compound, these patients developed symptoms within a week of exposure to the drug and followed a course of acute or subacute yellow atrophy, with associated pathologic findings.

Turning to the pathologic findings, the distinctive features were the obstructive type of biliary cirrhosis and the distribution of lipid deposits throughout the body. The lack of proliferation of bile ducts and, indeed, their apparent disappearance from the abundant periportal connective tissue suggests that the obstruction must have occurred above that level, probably in the finest cholangioles. Whether or not the lack of bile duct proliferation in the periportal connective tissue was the cause or effect of this obstruction is impossible to say. The progressive nature of the disease can be seen by comparison of the biopsy and post-

mortem material. The amount of connective tissue, bile stasis and focal areas of bile necrosis of liver cells increased markedly in the two years which elapsed between biopsy and death. (Fig. 6.)

The similarity between the clinical and laboratory findings in this case and those described by Hanger and Gutman[4] following the administration of arsphenamine is striking. With the appearance of xanthomas the syndrome meets all the criteria for the diagnosis of xanthomatous biliary cirrhosis; however, the sequence of development of chemical abnormalities in the blood seems to exclude the possibility of a primary disturbance in lipid metabolism, the intrahepatic obstructive lesion apparently developing first and the elevation of serum cholesterol to very high levels following. The case also corresponds to some of those collected by Hanot[9] to demonstrate that a hypertrophic form of liver disease may arise without antecedent obstruction to the extrahepatic biliary tract. This case might be likened to numbers 12, 13 or 15 of his series, with obstructive jaundice present for five years or more.

Sustained hypercholesterolemia over a period of years in this patient afforded an opportunity to compare the sites of lipid deposition in blood vessels with those observed in animals whose serum cholesterol levels had been elevated for the purpose of producing arteriosclerosis. The extensive sclerosis in the pulmonary arteries in the absence of pulmonary disease is reminiscent of that seen in rabbits fed or injected with cholesterol. The large amount of lipid in the spleen and kidney tubules as well as in the usual sites in the arteries and arterioles was similar to that observed both in dogs and rabbits in experimental arteriosclerosis.[10,11] Lipid in the parenchymal cells of the liver was much less marked than usually seen in animals, although comparable to those animals having cholesterol levels only two to three times above baseline values for long periods. Deposition of lipid in the endocardium of the left ventricle has been recorded by Thannhauser[1] as occurring in xanthomatosis of the hypercholesterolemic type but is not mentioned elsewhere in the literature.

SUMMARY

A case is presented, with postmortem findings, of cholangiolitic cirrhosis characterized by protracted intrahepatic biliary tract obstruction and associated with hypercholesterolemia, xanthomatosis and atheromatosis. While the clinical picture was that of xanthomatous biliary cirrhosis, the sequence of events does not indicate a primary disturbance in lipid metabolism with secondary liver disease. The cause of the liver disease was not established.

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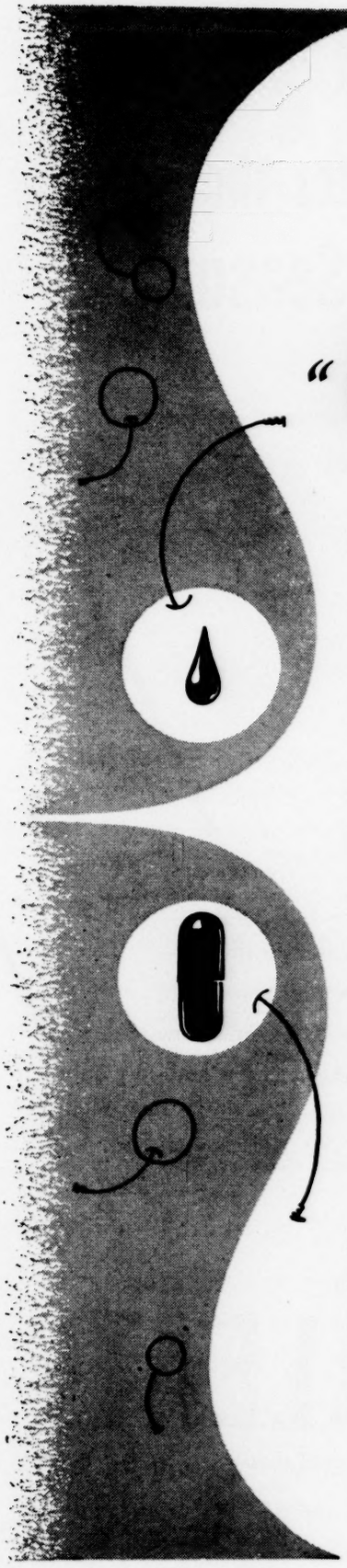


Complete Stability...

Outstanding Palatability...

"Choline (Flint)"

Continued patient acceptance of choline over prolonged periods can be assured by prescribing—

"Syrup Choline" (Flint)

25 per cent W/V—containing one gram of choline dihydrogen citrate in each 4 cc. Supplied in pints and gallons.

"Capsules Choline" (Flint)

containing 0.5 gram of choline dihydrogen citrate. Supplied in bottles of 100, 500 and 1000.

"Choline (Flint)" is indicated in fatty infiltrations of the liver associated with alcoholism, infectious hepatitis, early cirrhosis, diabetes, malnutrition.

For your copy of "The Present Status of Choline Therapy in Liver Dysfunction" write—

Flint, Eaton & Company

DECATUR, ILLINOIS

PROMPT RELIEF for the "Sneezin' Season"...

ORAL anti-histaminic treatment of hay fever and other common allergic manifestations is now accepted practice. In a recent study[1], the Pyra-Maleate formula (pyranisamine maleate) provided prompt symptomatic relief in the following percent of cases: hay fever—69.8%, vasomotor rhinitis—59.1%, acute urticaria—100%, pruritus—100%, angioneurotic edema—100%, and contact dermatitis—100%. Relatively few and only mild side effects were experienced.

VANPELT & BROWN, INC., Richmond, Va.

[1] *Annals of Allergy, 5:770:49*

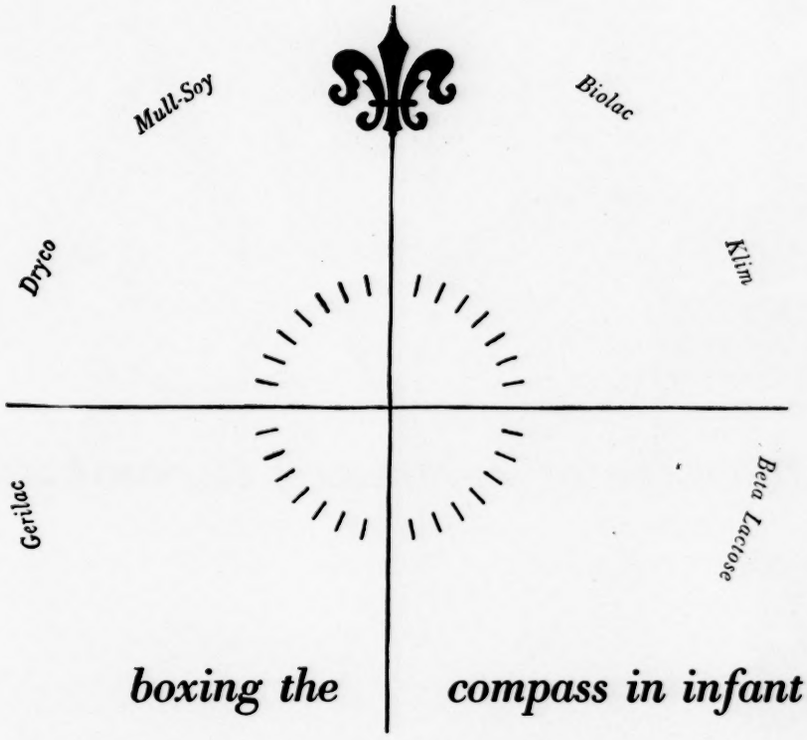
●

DOSAGE—the recommended average adult dose is one 50 mg. tablet 3-4 times daily; children one-half as much.

SUPPLIED—in 25 mg. and 50 mg. tablets in bottles of 30, 100 and 1,000.

PYRA-MALEATE

(Brand of Pyranisamine Maleate)



boxing the compass in infant nutrition

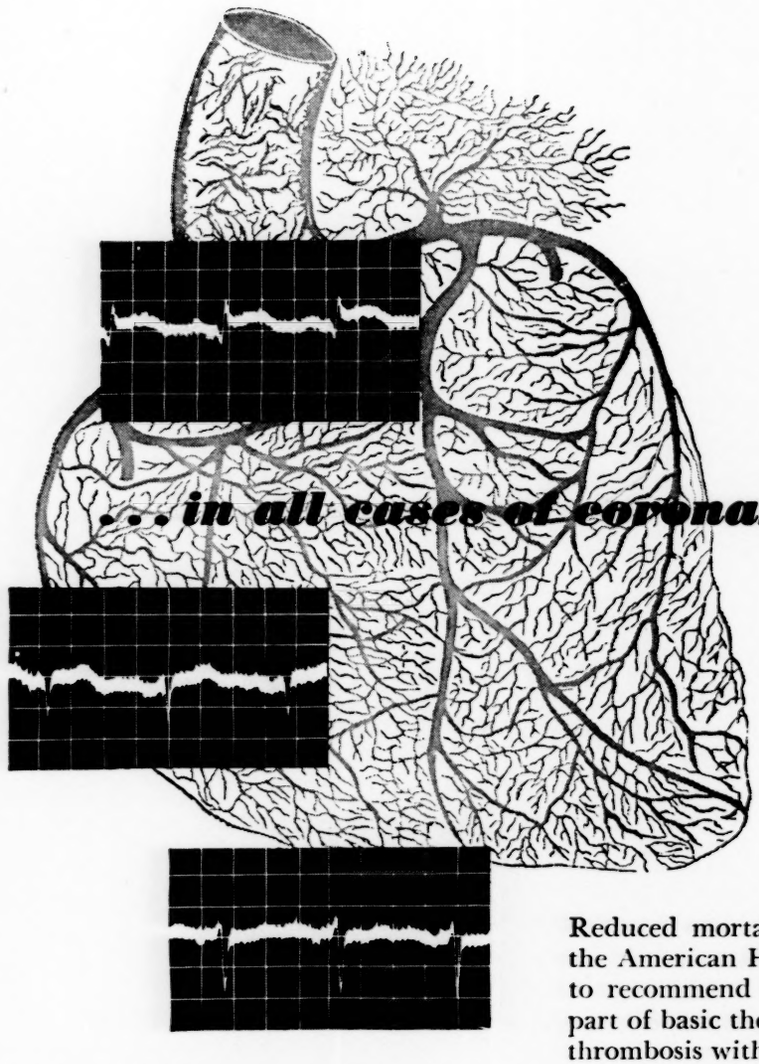
North, East, South, West—for every type of nutritional requirement, there is a Borden prescription product scientifically designed to meet the problem.

BIOLAC, Borden's improved, evaporated-type liquid modified milk, provides for all the known nutritional needs of early infancy except vitamin C.

DRYCO, a high-protein, low-fat powdered milk, serves as a valuable food in itself and as a versatile base assuring ample protein intake plus vitamins A and D. MULL-SOY is the answer to milk allergies—an emulsified hypo-allergenic soy food approximating milk. GERILAC, a spray-dried whole milk and skim milk powder, supplies elderly patients with high quality protein, calcium and iron, and also vitamins A, D, B and C. BETA LACTOSE promotes normal intestinal flora and acidity when used as a carbohydrate modifier. KLIM is powdered pasteurized whole milk, spray-dried for rapid solubility, convenient in hot climates and during travel.

These Borden products conform to the requirements of the Council on Foods and Nutrition and the Advertising Committee of the American Medical Association and are available only in pharmacies. We welcome inquiries from physicians. Write for professional literature and attractive practical Recipe Books.

The Borden Company, Prescription Products Division
350 Madison Avenue, New York 17



. . . in all cases of coronary thrombosis

Reduced mortality and morbidity have led the American Heart Association study group to recommend the use of anticoagulants as part of basic therapy "in all cases of coronary thrombosis with myocardial infarction."[1]

Long-acting Depo*-Heparin preparations meet the clinical requirements for prompt and readily controlled anticoagulant effects in the treatment of coronary heart disease. Depo-Heparin Sodium, with or without vasoconstrictors, provides the natural anticoagulant in a gelatin and dextrose vehicle to produce anticoagulant effects for 24 hours or longer with a single injection.

Methods of extraction, purification and assay have been so perfected by recent investigations of Upjohn research workers that Depo-Heparin is now available in full clinical supply.

1. Wright, et al: Am. Heart J. 36, 801 (Dec.) 1948.

**Trademark, Reg. U. S. Pat. Off.*

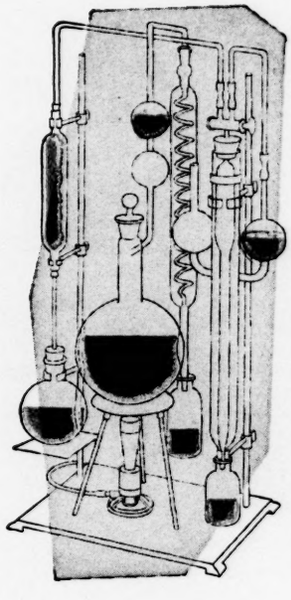
Upjohn ***Medicine . . . Produced with care . . . Designed for health***

THE UPJOHN COMPANY, KALAMAZOO 99, MICHIGAN

AUREO-MYCIN

in Surgical and Other Infections

AUREOMYCIN



Surgeons are now generally coming to the conclusion that the use of aureomycin preoperatively and postoperatively in all cases is worthwhile insurance against infection. This is particularly true in infections involving the peritoneum.

Aureomycin has also been found effective for the control of the following infections: African tick-bite fever, acute amebiasis, bacterial and virus-like infections of the eye, bacteroides septicemia, boutonneuse fever, acute brucellosis, Gram-positive infections (including those caused by streptococci, staphylococci, and pneumococci), Gram-negative infections (including those caused by the coli-aerogenes group), granuloma inguinale, *H. influenzae* infections, lymphogranuloma venereum, primary atypical pneumonia, psittacosis (parrot fever), Q fever, rickettsialpox, Rocky Mountain spotted fever, subacute bacterial endocarditis resistant to penicillin, tularemia and typhus.

Capsules: Bottles of 25, 50 mg. each capsule.
Bottles of 16, 250 mg. each capsule.

Ophthalmic: Vials of 25 mg. with dropper; solution prepared by adding 5 cc. of distilled water.

LEDERLE LABORATORIES DIVISION AMERICAN Cyanamid COMPANY 30 Rockefeller Plaza, New York 20, N. Y.

Control in urinary-tract infections...with

MANDELAMINE®

[BRAND OF METHENAMINE MANDELATE]

Adequate clinical use has established that **MANDELAMINE*** (methenamine mandelate) is effective against a wide range of organisms found in such urinary-tract infections as pyelitis, pyelonephritis, nephroptosis with pyelitis, cystitis, prostatitis, nonspecific urethritis, and infections associated with urinary calculi or neurogenic bladder.

In a recent report, Wilhelm et al.[1] underscore the positive antibacterial effectiveness of **MANDELAMINE** in the management of urinary-tract infections due to A. aerogenes—recognized as particularly resistant.

MANDELAMINE is distinguished for its virtual absence of the side-effects and drug-fastness so commonly associated with urinary antisepsis.

6 OUTSTANDING ADVANTAGES OF MANDELAMINE

1 Wide antibacterial range—including both gram-negative and gram-positive organisms
2 No supplementary acidification required (except when urea-splitting organisms occur)
3 Little or no danger of drug-fastness
4 Exceptionally well tolerated
5 No dietary or fluid regulation
6 Simplicity of regimen—3 or 4 tablets t.i.d.

SUPPLIED: Bottles containing 120, 500, and 1,000 enteric-coated tablets; each tablet 0.25 Gm. Literature and samples on request.

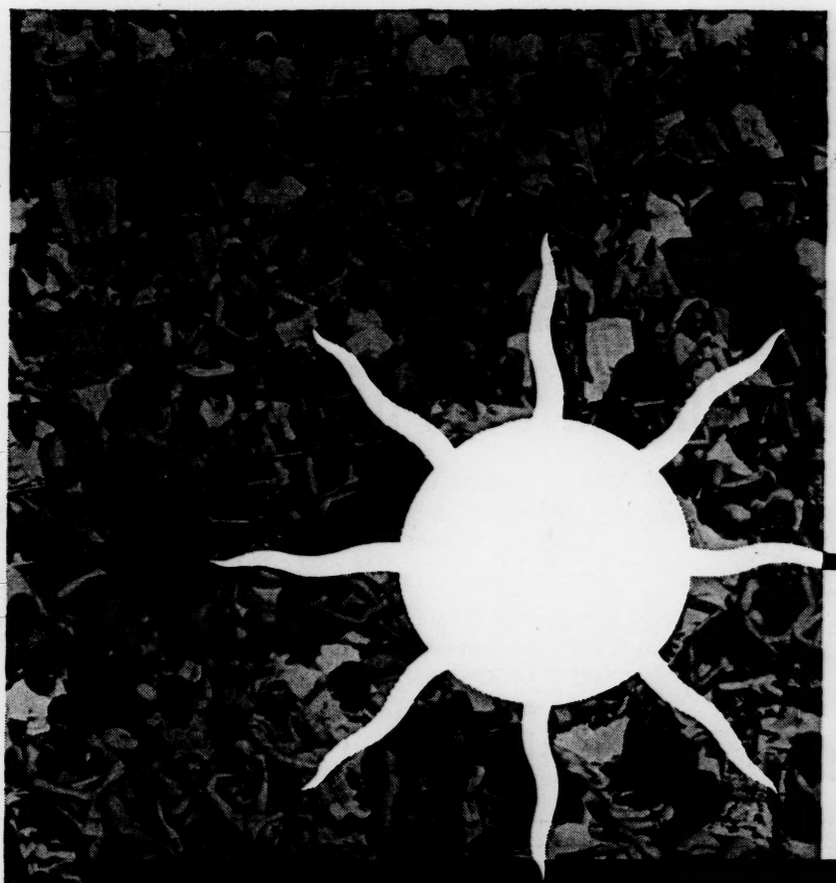
1. Wilhelm, S. F.; et al.: J.A.M.A. 141: 837 (Nov. 19) 1949.

NEPERA CHEMICAL CO., INC.

Pharmaceutical Manufacturers

NEPERA PARK, YONKERS 2, N. Y.

*MANDELAMINE is the registered trademark of Nepera Chemical Co., Inc., for its brand of methenamine mandelate.



For Prompt Relief

Cream

NEOHETRAMINE®

Hydrochloride

The soothing antihistaminic in cream form for the relief of itching due to sunburn, insect bites, and ivy poisoning.

SIMPLE TO USE: Rub gently into affected areas. CREAM NEOHETRAMINE HYDROCHLORIDE, 2% in 1 oz. tubes.

Neohetramine is the registered trademark of the Nepera Chemical Co., for its brand of thonzylamine—N, N-dimethyl-N' p-methoxybenzyl-N' (2-pyrimidyl) ethylenediamine.

Wyeth Incorporated • Philadelphia 3, Pa.

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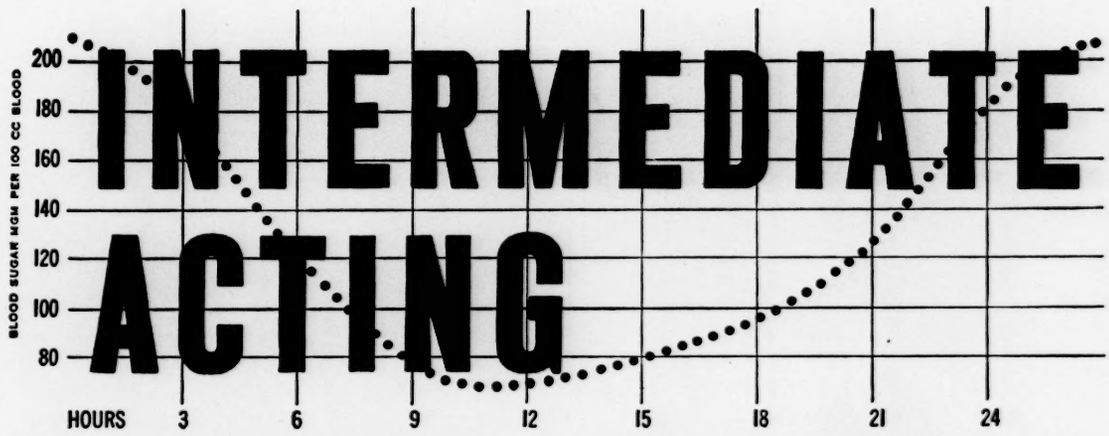


INTERMEDIATE ACTING

GLOBIN INSULIN

'B.W.& CO.'

...was developed to fill the "need for an insulin with activity intermediate between that of regular insulin and that of protamine zinc insulin."[1]

IN 1939, Reiner, Searle and Lang described a new "intermediate acting" insulin.

IN 1943, after successful clinical testing, the new substance was released to the profession as 'Wellcome' brand Globin Insulin with Zinc 'B.W. & Co.'

TODAY, according to Rohr and Colwell, "Fully 80% of all severe diabetics can be balanced satisfactorily"[2] with Globin Insulin 'B.W. & Co.'—or with a 2:1 mixture of regular insulin: protamine zinc insulin. *Ready-to-use* Globin Insulin 'B.W. & Co.' provides the desired intermediate action without preliminary mixing in vial or syringe.

In 10 cc. vials, U-40 and U-80.

1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. ibid Proc. Am. Diabetes Assn. 8:37, 1948.

'B.W.& CO. —a mark to remember

BURROUGHS WELLCOME & CO. (U.S.A.) INC. Tuckahoe 7, New York

She's heard the call for

VI-DAYLIN

TRADE MARK

(Homogenized Mixture of Vitamins A, D, B_1, B_2, C and Nicotinamide, Abbott)

THE *quickest* route home is the one children take when vitamin time means VI-DAYLIN. For this multivitamin treat embodies all the appeal of sparkling yellow honey, all the tasty goodness of lemon candy, with the pleasant aroma of fresh citrus fruit. There's no need to disguise VI-DAYLIN—children like it right from the spoon.

The potent VI-DAYLIN formula comprises six essential vitamins in a homogenized mixture that is stable without refrigeration.

Mixes with milk, cereal and other foods for infants. And VI-DAYLIN leaves no resistant stains on clothing, has no fishy odor.

Available in 90-cc., 8-fluidounce and 1-pint bottles. Abbott

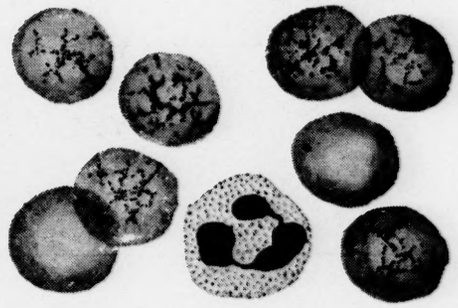
See the Formula

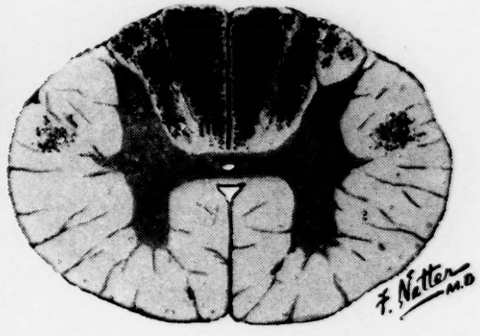
Each 5-cc. teaspoonful of Vi-Daylin contains:

Vitamin A	3000 U.S.P. units
Vitamin D	800 U.S.P. units
Thiamine Hydrochloride	1.5 mg.
Riboflavin	1.2 mg.
Ascorbic Acid	40 mg.
Nicotinamide	10 mg.

IS THERE A SUBSTITUTE FOR LIVER IN PERNICIOUS ANEMIA?

To induce hemopoietic response





To prevent spinal cord degeneration

With the discovery of B_{12} another important hemopoietic factor present in liver is established.

No substitutes for quality liver preparations in the treatment of pernicious anemia have been confirmed, but B_{12} offers a substitute for liver therapy in treating those pernicious anemia patients who exhibit a sensitivity to liver extract. It also offers an important adjunct to liver therapy in treating pernicious anemia, nutritional macrocytic anemia, nontropical sprue and tropical sprue.

B_{12} Concentrate Armour is available in 10 cc. multiple dose vials (each cc. contains 10 micrograms of vitamin B_{12}.)

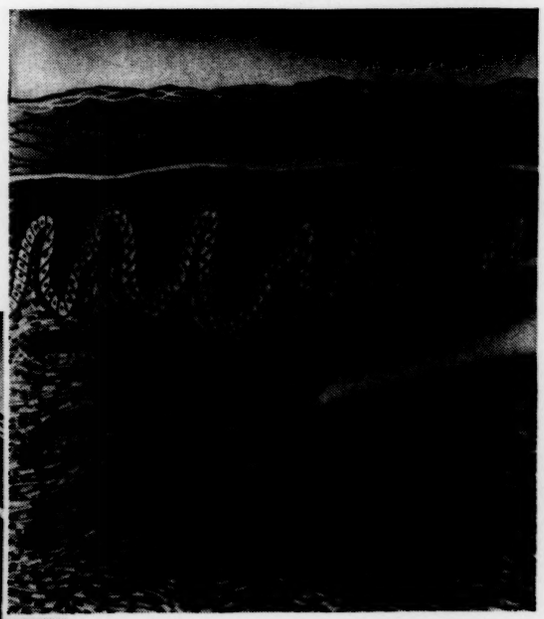
Have confidence in the preparation you prescribe or administer—"specify Armour."

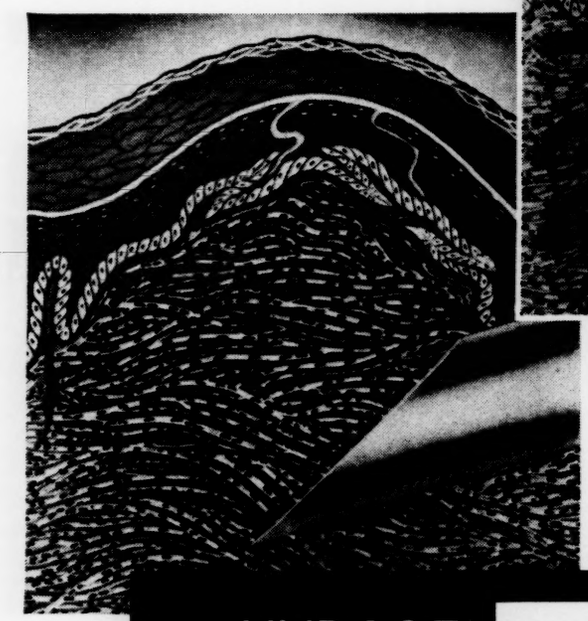
ARMOUR *Laboratories*

HEADQUARTERS FOR MEDICINALS OF ANIMAL ORIGIN • CHICAGO 9, ILLINOIS

HYPODERMOCLYSIS

with HYDASE





without HYDASE

HYDASE*

Lyophilized Hyaluronidase

Wyeth

Highly Purified

For speedy absorption of fluids in hypodermoclysis. Prevents pain from stretching of tissue—nontoxic and apparently nonallergenic.

For More Complete and Widespread Local Anesthesia—fewer injections of local anesthetics required.

HYDASE in dry form is stable indefinitely; keeps in sterile solution for 2 weeks—refrigeration unnecessary.

SUPPLIED: Vials of 150 and 500 turbidity reducing (TR) units.

*Trade Mark

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